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Abstract: Newly diagnosed glioblastoma is now commonly treated with surgery, if feasible, or biopsy, followed by radiation plus concomitant and adjuvant temozolomide. The treatment of recurrent glioblastoma continues to be a moving target as new therapeutic principles enrich the standards of care for newly diagnosed disease. We reviewed PubMed and American Society of Clinical Oncology abstracts from January 2006 to January 2012 to identify clinical trials investigating the treatment of recurrent or progressive glioblastoma with nitrosoureas, temozolomide, bevacizumab, and/or combinations of these agents. At recurrence, a minority of patients are eligible for second surgery or reirradiation, based on appropriate patient selection. In temozolomide-pretreated patients, progression-free survival rates at 6 months of 20%-30% may be achieved either with nitrosoureas, temozolomide in various dosing regimens, or bevacizumab. Combination regimens among these agents or with other drugs have not produced evidence for superior activity but commonly produce more toxicity. More research is needed to better define patient profiles that predict benefit from the limited therapeutic options available after the current standard of care has failed.

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Standards of care for treatment of recurrent glioblastoma—are we there yet?

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ABSTRACT [<250 words]

Introduction

Newly diagnosed glioblastoma is now commonly treated with surgery as feasible or biopsy, followed by radiotherapy plus concomitant and adjuvant temozolomide. The treatment of recurrent glioblastoma continues to be a moving target as new therapeutic principles enrich the standards of care for newly diagnosed disease.

Methods

We reviewed PubMed and ASCO abstracts from 2006 to January 2012 to identify clinical trials investigating the treatment of recurrent or progressive glioblastoma with nitrosoureas, temozolomide, bevacizumab, and/or combinations of these agents.

Results

At recurrence, a minority of patients are eligible for second surgery or reirradiation, based on appropriate patient selection. In temozolomide-pretreated patients, progression-free survival rates at 6 months of 20% to 30% may be achieved either with nitrosoureas, temozolomide in various dosing regimens, or bevacizumab. Combination regimens among these agents or with other drugs have not produced evidence for superior activity, but commonly more toxicity.

Conclusion

More research is needed to better define patient profiles that predict benefit from the limited therapeutic options available after the current standard of care has failed.

Keywords: bevacizumab, glioblastoma, nitrosoureas, MGMT, temozolomide.

INTRODUCTION

Glioblastoma is the most aggressive malignant primary brain tumor in adults (median age, 64 years) with a preponderance in males (1.3 to 1.6:1) and whites and those of European descent (2:1 compared with African Americans).[1,2] The annual incidence ranges from 3 to 5 newly diagnosed cases per 100 000 population. Therapeutic advances over the last decade have led to improvements in both patients' life expectancy and quality of life. Based on data from the Surveillance, Epidemiology and End Results (SEER) program, median survival times of all patients with newly diagnosed glioblastoma improved from 8.1 months in 2000 to 2003 to 9.7 months in 2005 to 2008, likely due to the introduction of temozolomide.[3]

The current standard of care for patients with newly diagnosed glioblastoma was established in 2005, following the pivotal European Organization for the Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) trial, where concurrent temozolomide (75 mg/m^2/daily for up to 7 weeks) and radiotherapy followed by 6 maintenance cycles of adjuvant chemotherapy (150-200 mg/m^2 5-day therapy every 28 days) led to improved progression-free survival (PFS) and overall survival (OS).[4] Improved survival in this trial was largely restricted to a subset of patients harboring promoter methylation of the DNA repair gene O^6-methylguanine-DNA methyltransferase (MGMT).[5] In a recent phase 3 trial of 833 eligible patients, no significant improvement in median OS (16.6 vs 14.9 mo; $P = 0.63$) or median PFS (5.5 vs 6.7 month; $P = 0.06$) was found for patients who received dose-dense extended temozolomide (75 mg/m^2 21-day therapy every 4 weeks for 6-12 cycles) plus radiotherapy compared with patients who received standard-dose temozolomide plus radiotherapy, respectively, regardless of methylation status.[6] However,

MGMT promoter methylation was associated with improved median PFS (8.7 vs 5.7 months; $P < 0.0001$) and OS (21.2 vs 14 months; $P < 0.0001$).[6] Despite standard of care therapy,[7] recurrence rates remain high in patients with glioblastoma (~90%). Median OS is 15 to 18 months in clinical trial populations, and <10% are alive at 5 years.[1]

The primary purpose of this paper is to discuss the role of second-line monotherapy and combination therapies for patients with recurrent or progressive glioblastoma. What is the current role of nitrosoureas, alone or in combination? Does efficacy outweigh their toxicity profile? We will also address the efficacy of the varied metronomic temozolomide dosing regimens for rechallenge (ie, patients re-exposed to temozolomide who had been previously treated, or patients switched to alternative dosing regimens of temozolomide following signs of relapse or progression on standard temozolomide therapeutic regimens) as well as for temozolomide-naïve patients. The availability of bevacizumab, alone or in combination, to treat recurrent disease is another relatively new option that requires perspective.

Numerous other issues must be considered when attempting to establish a standard of care for patients with recurrent glioblastoma. How is recurrence best determined? Which patients qualify for second surgery or repeat radiotherapy? Which patients should not be retreated at all? How should efficacy of treatment for recurrent glioblastoma be assessed in clinical trials? Is 6-month PFS the optimal end point? Also, the prognostic value of the *MGMT* status in patients with recurrent glioblastoma is not well defined. Does *MGMT* status guide the selection of the appropriate agent at recurrence? Are other markers useful?

Diagnosis of Progression

Neuroimaging (serial MRI) remains the primary monitoring tool for glioblastoma with

assessments typically performed every 2 to 3 months during treatment and somewhat longer intervals during disease progression-free periods. However, standard MRI contrast studies, even when adhering to Macdonald criteria,[8] may be misleading and confound the diagnosis of recurrence. Within the first months following completion of radiotherapy and concomitant temozolomide, it can be difficult to distinguish recurrence from pseudoprogression when using typical MRI modalities, e.g., T2, T1 with gadolinium, and fluid-attenuated inversion recovery (FLAIR).[9] Pseudoprogression refers to an apparent increase in the tumor size that does not reflect tumor progression biologically and can only be proven post hoc if no further tumor-specific treatment is administered at the time point of pseudoprogression and the lesion subsequently regresses. MRI patterns suggestive of pseudoprogression have been described in 20% to 30% of patients treated with RT/TMZ→TMZ.[10,11] Furthermore, radionecrosis characterized by blood-brain barrier disruption, edema, and mass effect mimicking progression appears earlier in these patients versus those treated with radiotherapy alone.[11] Both pseudoprogression and radionecrosis are likely related and consistent with the increased tumor cell killing caused by chemoradiotherapy or increased host normal tissue responses, including blood-brain barrier breakdown, ischemia, effects of steroid withdrawal, and inflammation.[9] Nonetheless, the recurrence of glioblastoma remains predominantly local.[12,13]

Currently, the roles of single photon emission-computed tomography (SPECT), positron emission tomography (PET), MR spectroscopy, and functional MRI in determining progression are being evaluated At present, we would advocate careful reimaging in case of suspected pseudoprogression. With no or minimal new symptoms, any rapid change of treatment is discouraged. Ultimately, some patients may need a biopsy if a definitive diagnosis needs to be established. In any case, before diagnosing pseudoprogression, it must be ascertained whether

the scans selected for comparison are appropriate, eg, a postsurgical scan may not be useful to assess progression at the first scan after concomitant radiochemotherapy if that patient started radiotherapy only 4 to 6 weeks after surgery. Moreover, the first scan after radiochemotherapy should be considered as a new baseline for all further imaging assessments.

Radiographic Assessment of Treatment Response

Efficacy evaluation of treatment in recurrent glioblastoma commonly relies on neuroimaging, supported by clinical monitoring, but can be complicated. A complete resolution of blood-brain disturbance detected by contrast extravasation on MRI or CT will no longer qualify as a response if there is increased T2 or FLAIR abnormality. Such responses are now referred to as "pseudoresponses." The new Response Assessment in Neuro-Oncology (RANO) criteria, which integrate at least a qualitative measure for T2/FLAIR changes, appear to be an improvement over the Macdonald criteria and may facilitate the interpretation of therapeutic outcomes in patients with glioblastoma (Table 1).[14,15] In contrast to the Macdonald criteria, measurable and nonmeasurable lesions are defined, and tumor size is measured on T2-/FLAIR-weighted images in addition to the contrast-enhancing tumor. The RANO criteria also establish criteria for entry into clinical trials for recurrent high-grade glioma. For a first progression that allows screening for a recurrent therapy trial, time from initial chemoradiotherapy is pivotal. Patients will not be formally considered progressors within the first 3 months from the end of radiochemotherapy. Also, RANO criteria provide definitions of radiographic response that incorporate changes in non-enhancing lesions. For suspected cases of pseudoprogression not only in the context of temozolomide-based radiochemotherapy, but also in new therapies, notably local therapies, that influence the vascular biology of malignant gliomas, a close control MRI and clinical

examination are recommended. The RANO criteria are likely to be valuable when assessing treatment response in clinical trials as well as for monitoring patients in daily practice, but will require further validation.

Role of Repeat Surgery and Radiotherapy

About 1 in 4 patients with progressive or recurrent glioblastoma can be considered for repeat surgery. The benefits of reoperation have primarily been derived from retrospective studies. A more favorable prognosis following surgery for recurrence or progression is associated with younger age (<70 years), smaller tumor volume (<50 cm^3), and a preoperative KPS >80%.[16,17] Repeat surgery is not recommended for patients with involvement of prespecified eloquent/critical brain regions.[17] A controversial practice at the time of repeat surgery is the implantation of biodegradable chemotherapy wafers containing carmustine, which may prolong survival, but are rarely used today.[7,18]

Reirradiation remains a palliative option for a select group of patients with recurrent glioblastoma. Patients with a KPS of >60%, a tumor size of <30 to 40 mm, and progression >6 months from time of surgery appear to be the best candidates.[19] The most common approach involves the use of fractionated stereotactic radiotherapy with or without intensity modulation and a median total dose of 30 to 36 Gy.[20] In contrast, stereotactic radiosurgery, the administration of one single fraction, which has the theoretical advantage of sparing normal tissue, is rarely used in glioblastoma because of the poorly defined target volume. Interestingly, none of the reirradiation schedules has ever been looked at in a prospective or controlled fashion. In fact, the recent APG101 trial provided no sign of efficacy for reirradiation at 18 x 2 Gy in recurrent glioblastoma patients commonly deemed best candidates for that intervention.[21]

Monotherapy and Combination Chemotherapeutic Trials for Recurrent Disease

Over the last decade, an increased number of clinical trials have evaluated the benefits of single agent and combination chemotherapy to treat patients with recurrent or progressive glioblastoma. Older studies usually evaluated a heterogeneous patient population, including those with a mix of WHO grade III/IV gliomas. Older series often reported on therapeutic options in temozolomide-naïve patients, whereas more recent studies included only those pretreated with temozolomide. Almost all study designs were noncomparative or failed to include an adequate control arm. The majority considered 6-month PFS rate and median OS from the time of recurrence as the primary end points. Although the 6-month PFS rate is advocated as a reliable measure of tumor control and a strong predictor of survival,[22] it is influenced by further salvage therapies. Radiographic responses were often incompletely reported with most studies using the Macdonald criteria to assess response. Finally, interpretation of efficacy findings, specifically comparison between independent publications, may be confounded by other factors, including whether reirradiation or repeat surgery were performed as well as number of previous relapses, general health status, age, and other underlying factors.

This report is a systematic review, which used PubMed and ASCO abstract reports from 2006 to January 2012 as the primary sources of data. The objective of the analysis was to identify clinical efficacy trials following systemic treatment with nitrosoureas, temozolomide, bevacizumab, and/or combinations of these agents in patients with recurrent or progressive glioblastoma. No specific limitations were placed on the selection of studies given the relative paucity of data.

Nitrosoureas—single and combination therapy. Nitrosoureas are DNA alkylating agents characterized by high lipophilicity, which permit blood-brain barrier penetration, making them useful in the treatment of brain tumors. Prior to 1999, nitrosoureas (eg, carmustine [BCNU], lomustine [CCNU] and nimustine [ACNU]) were commonly used in the first-line treatment of glioblastoma. Another alkylating agent, procarbazine, was used alone or in combination with CCNU. In 1999, two phase 2 trials changed the therapeutic landscape when temozolomide was found to be efficacious for recurrent glioblastoma patients who had received no more than 1 course of nitrosourea-based chemotherapy.[23,24] These data, coupled with the favorable tolerability profile of temozolomide, led to its approval in 1999 for recurrent high-grade gliomas, and nitrosoureas were moved into second line. Subsequently, temozolomide became the treatment of choice for newly diagnosed glioblastoma in 2005. Despite the less than optimal safety profile of nitrosoureas, e.g., bone marrow suppression, liver/renal toxicity, and interstitial lung disease, they remain a second-line treatment option in single and combination regimens for recurrent disease (Table 2).

Two phase 2 trials[25,26] and 1 retrospective series[27] evaluated a similar carmustine monotherapy regimen for recurrent/progressive disease in 104 patients, some of whom had received prior temozolomide therapy. The 6-month PFS and median OS for 2 studies ranged from 13.0% to 17.5% and 5.1 to 7.5 months, respectively; no complete remissions were observed.[26,27] Efficacy end points for one study were unevaluable (data not presented separately for carmustine).[25] The predominant side effects following carmustine monotherapy were hematologic and long-lasting hepatic and pulmonary toxicity (Table 2).

A recent prospective phase 3 trial in 92 lomustine-treated patients (70 at first relapse) reported a 19% 6-month PFS response rate with a median OS of 7.1 months.[28] Grade 3 and 4

hematologic toxicities were very common (46 events) with thrombocytopenia and neutropenia reported most often. In a double-blind, randomized, multicenter phase 3 trial of 325 patients who received prior radiation and temozolomide, the lomustine monotherapy arm (n = 65) provided a 6-month PFS rate and median OS of 24.5% and 9.8 months.[29,30] Grade 3 and 4 thrombocytopenia, leukopenia and lymphopenia were common.

In a small retrospective report, nimustine (ACNU) in temozolomide-pretreated patients was given alone (n = 14) or in combination with teniposide (n = 17) or cytarabine (n = 1).[31] The 6-month PFS rate for all 32 patients was 20%, and the median OS from the start of nimustine therapy was 6.7 months. Fifty percent of patients developed grade 3 or 4 hematologic toxicity. No patient developed pulmonary fibrosis.

Fotemustine is another nitrosourea compound mostly studied in Europe, notably Italy and France.[32] Four prospective phase 2 trials, using slightly different induction/maintenance dosage regimens, evaluated fotemustine in temozolomide-pretreated patients with recurrent or progressive glioblastoma.[33-36] Two studies were exclusively in patients experiencing their first relapse.[33,35] Overall, 6-month PFS and median OS ranged from 20.9% to 61% and 6.0 to 11.1 months, respectively. The best findings were obtained with a protracted low-dose induction regimen and the administration of fotemustine at least 3 months after completing first-line temozolomide therapy.[33] Grade 3 and 4 hematologic toxicities were commonly reported following fotemustine therapy; however, lower rates were observed[33] perhaps due to the implementation of a longer rest period (2 weeks) between doses during the induction phase. The small sample sizes in each of these studies call for larger prospective trials to ascertain the efficacy and safety of fotemustine in a temozolomide-pretreated population with recurrent glioblastoma.

Little data are published that assess nitrosourea combination therapies for recurrent disease. Two retrospective studies (1994-2003), encompassing nearly 150 patients of whom 16 received front-line temozolomide, evaluated the combination of procarbazine, lomustine, and vincristine.[37,38] Similar efficacy findings were reported in the 2 reports: 30% to 38% PFS at 6 months and 7.6 to 7.9 months OS. While grade 3/4 hematologic toxicity was common (26%), nonhematologic toxicity was mild, and pulmonary fibrosis was not reported.[37] Lomustine in combination with cediranib (n = 129) was not found to be more effective (6-month PFS, 34.5%; median OS, 9.4 months) than lomustine given alone (see above).[29,30] However, grade 3 and 4 hematologic and nonhematologic toxicities were substantially greater with combination versus either monotherapy arm.

Significant hematologic toxicity concerns and the availability of more effective agents have made the use of nitrosoureas overall less desirable. New schedules at lower doses may prove beneficial. The nitrosoureas seem comparable in terms of efficacy at clinically tolerated doses, whereas nonhematologic toxicity, notably lung fibrosis, may be more common with carmustine than with lomustine or nimustine.

Temozolomide monotherapy trials. Numerous trials have evaluated the efficacy and safety of temozolomide as monotherapy for recurrent or progressive disease, albeit few of the trials were conducted as prospective randomized controlled designs (Table 3).

Nine trials evaluated temozolomide monotherapy given in traditional (5-day/cycle) and novel schedules in 372 temozolomide-naïve patients with recurrent disease.[24,39-46] Generally, patients were being treated for first or second relapses. Approximately half of the patients had received previous chemotherapy, mostly nitrosourea-based; the remainder was managed with

surgery and radiotherapy as first-line treatment. Five of these studies administered temozolomide in traditional 5-day/cycle regimens with doses ranging from 150 to 200 mg/m^2.[24,39,40,42,44] Novel metronomic temozolomide schedules (75-100 mg/m^2 once or twice a day for 21-42 consecutive days using 28- to 70-day cycles) were used in 3 studies. [41,43,45]. A 1-week-on/1-week-off schedule of temozolomide 150 mg/m^2 was investigated in one study, in which promising 6-month PFS rates approaching 50% were observed.[46,47] Across all 9 studies, 6-month PFS rates ranged from 18% to 48% and median OS was 5.4 to 9.9 months. Notably, survival appeared higher by about 2 months in the more recent studies,[43-45] which may be due to other changes in the standard of care of glioblastoma patients or due to patient selection.

Six studies, conducted in 162 temozolomide-pretreated patients, evaluated temozolomide rechallenge.[48-53] A variety of metronomic schedules were employed, including 40 to 100 mg/m^2 daily doses given for 21 to 365 consecutive days as well as alternating 1-week-on/1-week-off regimens. Overall, the 6-month PFS rate and median OS ranged from 23% to 58.3% and 5.1 to 13 months, respectively.

One retrospective analysis compiled data on 5 different temozolomide dosing regimens among 47 patients (re)challenged while receiving adjuvant temozolomide or after a temozolomide-free interval (Table 3).[54] The 6-month PFS rates were 26.3% and 28.6% for patients progressing on temozolomide versus after temozolomide. The corresponding median OS was 6.6 and 5.3 months, respectively.

Of particular note, the RESCUE study examined the benefits of temozolomide rechallenge based on the "temozolomide-free interval", i.e., time between upfront treatment and rechallenge.[51] The 6-month PFS rate and median OS were 27.3% and 3.6 months for patients receiving rechallenge early (progression while receiving adjuvant temozolomide before

completion of 6 cycles of adjuvant temozolomide); 7.4% and 1.8 months for patients receiving rechallenge after an extended period (progression while receiving extended adjuvant temozolomide beyond the standard 6 cycles but before completion of adjuvant treatment); and 35.7% and 3.7 months for patients receiving rechallenge after a prolonged interval (progression after completion of adjuvant treatment and a treatment-free interval of greater than 2 months). Patients who experienced early progression derived the most benefit from temozolomide rechallenge therapy. The authors considered the possibility that the results in this early rechallenge group could be in part attributable to pseudoprogression but noted that the study was intentionally designed to exclude patients who progressed within the first 12 weeks following completion of chemoradiation, in keeping with the RANO criteria. Furthermore, the median time from the end of radiotherapy in this early group was 5.2 months, thus minimizing the influence of pseudoprogression on these results.

Three randomized clinical trials were conducted using single agent temozolomide.[23,55,56] In one study, a standard temozolomide regimen was more efficacious than procarbazine (6-month PFS, 21% vs 8%) with a median 1.5 month longer survival time.[23] The latter study was conducted in temozolomide-naïve patients and led to the approval of temozolomide for recurrent glioblastoma in Europe, although not in the United States. The BR12 study did not provide separate data for glioblastoma patients, but indicated that temozolomide dose-intense regimens do not provide a survival or PFS benefit compared with standard doses when treating temozolomide-naïve patients. The DIRECTOR trial evaluated 2 dose-intense regimens of temozolomide (ie, 120 mg/m^2/d 1 week on/1 week off vs 80 mg/m^2/d 3 weeks on/1 week off) in patients experiencing a first relapse after at least 2 cycles of temozolomide.[56] Specifically, patients were enrolled based on first progression of glioblastoma documented by MRI no earlier

than 180 days after first surgery and no earlier than 90 days after completion of radiotherapy. Data are currently maturing.

Toxicity following single agent temozolomide therapy after rechallenge is outlined in Table 3. Grade 3 and 4 hematologic adverse events were reported in most studies, although there was no evidence of cumulative toxicity. Considering the small numbers of patients in most studies and the wide range of temozolomide regimens tested, there was no evidence that one metronomic schedule was advantageous over another in terms of safety.

Bevacizumab monotherapy trials. Bevacizumab is a human recombinant monoclonal antibody to vascular endothelial growth factor (VEGF), a critical mediator of tumor angiogenesis.[57,58] Bevacizumab was approved in 2009 by the US FDA for the treatment of recurrent glioblastoma based on response rate with durable responses relative to historical controls from noncomparative phase 2 trials[59,60]; it is also available for use in various other countries throughout the world, but not in the European Union. The rejection in Europe was based on the absence of a randomized trial with a bevacizumab-free control arm.

Three prospective phase 2 trials and 1 retrospective analysis have evaluated bevacizumab monotherapy in 233 temozolomide pretreated patients with recurrent or progressive disease (Table 4).[59-62] Three studies used an identical dosing regimen (10 mg/kg IV every 2 weeks),[59,60,62] whereas one study administered 15 mg/kg every 3 weeks.[61] The 6-month PFS rate ranged from 25% to 42.6% with a median OS of 6.5 to 9.2 months (Table 4). Radiographic responses were encouraging with complete and partial responses reported in 62/183 patients (33.9%).[59,60,62] Grade 3 and 4 toxicity across the 4 studies was primarily nonhematologic and included hypertension, thromboembolic events, and fatigue. Prospective phase 3 studies would

be needed to determine more clearly the role of bevacizumab in the management of patients with recurrent or progressive glioblastoma. Meanwhile, data from two large randomized trials, AVAglio and RTOG-0825, adding bevacizumab to temozolomide chemoirradiation are likely to shape the future standards of care both at diagnosis and at recurrence.

Other antiangiogenic agents. Various novel agents targeting potential regulators critical to glioblastoma cell growth, invasion, and angiogenesis have been evaluated in phase 2 trials in patients with recurrent disease. The VEGFR inhibitor cediranib was explored in patients with recurrent glioblastoma in a very sophisticated fashion using advanced neuroimaging and biomarkers studies.[63,64] The PFS rate at 6 months of 31 patients with recurrent glioblastoma treated with cediranib monotherapy at a starting dose of 45 mg/d was 25.8%. Response rates were 56.7% for 3-dimensional measurements and 27% for 2-dimensional measurements. Toxicities were moderate. Changes in plasma placental growth factor, basic fibroblast growth factor, matrix metalloproteinase (MMP)-2, soluble VEGF receptor 1, stromal cell–derived factor-1, and soluble Tie2, and in urinary MMP-9/neutrophil gelatinase-associated lipocalin activity in response to cediranib were associated with radiographic response or survival.[64] Aflibercept (VEGF trap), a recombinant fusion protein that inhibits both VEGF and placental growth factor, was administered to 42 patients with recurrent glioblastoma at first relapse.[65] Efficacy of VEGF trap as a single agent for recurrent disease was minimal with a 6-month PFS rate of 7.7%, although 2 patients had durable response (alive at >150 weeks). Furthermore, grade 3 nonhematologic toxicity was common and included fatigue and hypertension. XL184, an inhibitor of MET, VEGFR2, and RET, was given PO (125 mg or 175 mg/d) to 124 patients with recurrent glioblastoma.[66] Modest activity was observed in patients with and without prior

antiangiogenic exposure. Overall, the interim 6-month PFS rates for the 125-mg and 175-mg cohorts were >25% and 21%, respectively.[67] The most common grade 3 and 4 toxicities were fatigue (23%), hypophosphatemia (10%), serum lipase elevation (10%), and ALT elevation, headache, lymphopenia, and convulsion (9% each).

Cilengitide, an inhibitor of αvβ3 and αvβ5 integrin receptors, showed modest single agent activity, i.e., 6-month PFS of 15% and median OS of 9.9 months, following a 2000 mg twice-daily continuous regimen among 40 patients with recurrent glioblastoma (Table 4).[68] Significant hematologic or nonhematologic toxicities following single agent cilengitide therapy were uncommon. Another phase 2 trial among 26 evaluable patients with recurrent glioblastoma also found that cilengitide was only modestly effective (ie, 6-month PFS of 12%).[69]

Temozolomide-containing combination trials. Over the last decade, more than a dozen phase 1 and 2 studies have investigated the efficacy and safety of temozolomide in combination with bevacizumab,[70,71] nitrosoureas,[72,73] and interferon[74] as well as a plethora of conventional/miscellaneous chemotherapeutic agents, e.g., irinotecan, pegylated doxorubicin, cisplatin, capecitabine or sorafenib, for recurrent or progressive glioblastoma (Table 5).[75-85] In general, the efficacy findings following temozolomide combination therapy failed to indicate a significant advantage over temozolomide or bevacizumab monotherapy regimens. However, evaluation of these studies is hampered by small sample sizes, heterogeneous study populations (temozolomide-naïve vs -pretreated; varied number of recurrences; number and type of prior therapies; time from last treatment to progression), and various temozolomide dosing regimens. Several recently conducted combination studies in temozolomide-pretreated patients deserve mention.

Desjardins and colleagues evaluated the combination of protracted temozolomide (50 mg/m^2 daily) and bevacizumab (10 mg/kg intravenously every 2 weeks) in 32 temozolomide-pretreated patients who predominantly were experiencing a first or second recurrence (94%).[71] A radiographic response (all partial) was observed in 9/32 (28%) patients. The 6-month PFS rate was 18.8% with a median OS of 8.7 months. Not surprisingly, patients not receiving dexamethasone had a significantly higher 6-month PFS rate compared with those receiving steroids (31.3% vs 6.3%; $P = 0.03$). No difference in survival was observed between patients who had experienced disease progression on 5-day temozolomide before enrollment versus those who did not progress on 5-day temozolomide. *MGMT* status, determined in 21 patients, did not appear to be related to outcome. The regimen was well tolerated and characterized primarily by nonhematologic toxicities; 2 patients discontinued therapy secondary to toxicity (prolonged thrombocytopenia and grade 4 pancreatitis).

Gaviani and colleagues evaluated the combination of temozolomide and fotemustine in 10 patients with recurrent disease following chemoradiation.[73] The study was terminated early (planned enrollment of 105) because of severe hematologic toxicities (predominantly grade 3 and 4 thrombocytopenia and granulocytopenia). The authors concluded that this combination does not merit further study.

A protracted daily temozolomide (50 mg/m^2 daily) plus sorafenib regimen had very limited activity, despite a good safety profile, in 32 patients with recurrent disease.[75] Only one patient achieved a partial response. The 6-month PFS rate was very low (9.4%). Importantly, ~50% of enrolled patients had 2 or more prior progressions and had progressed while receiving 5-day temozolomide, and more than one-third of patients had failed either prior bevacizumab or VEGFR inhibitor therapy. Despite potentially complementary direct and indirect mechanisms of

antitumor activity, the temozolomide/sorafenib combination was not effective in this phase 2 trial. The poor results may be attributed to heavy pretreatment, higher failure rate to previous bevacizumab therapy, lack of selection of patients with sorafenib target expression, and the relatively high use of CYP3A-inducing antiepileptic drugs that may have compromised sorafenib activity.

The combination of temozolomide and afatinib (40 mg/d), an irreversible blocker of the epidermal growth factor receptor, was investigated in a phase 2 study.[82] The 6-month PFS rate by independent review was 10% for the combination compared with 3% for patients receiving afatinib alone ($P = 0.008$) and 23% for patients given temozolomide alone ($P = 0.59$). Serious adverse events (≥ grade 3) for the combination were primarily nonhematologic (eg, diarrhea and skin reactions).

A retrospective study in 28 patients (of whom 24 received temozolomide pretreatment) found that the combination of continuous low-dose temozolomide (10 mg/m^2 twice daily) and celecoxib (200 mg daily) had some activity in treating recurrent glioblastoma without significant toxicity.[84] The majority of patients (86%) were being treated for their first recurrence. Notably, 19 (68%) patients underwent resection before retreatment. The 6-month PFS rate was 43%. *MGMT* promoter methylation did not predict a favorable outcome. The only severe toxicity was grade 3 lymphopenia in one patient.

The combination of temozolomide and O^6-benzylguanine, a MGMT-depleting agent, was tested in 34 patients with recurrent disease.[83] One patient responded to this regimen. The 6-month PFS rate was low (9%) with a median OS of 4.5 months. This 1-day temozolomide combination regimen failed to restore temozolomide sensitivity in patients with recurrent glioblastoma.

Overall, the temozolomide combination studies available to date do not suggest that one particular chemotherapy combination regimen is more effective than administration of temozolomide alone.

Bevacizumab-containing combination trials. In addition to the studies that evaluated bevacizumab in combination with temozolomide (see section above), another series of studies have been conducted, which evaluated bevacizumab and miscellaneous other agents, including irinotecan, carboplatin, etoposide, erlotinib, and cetuximab, in patients with recurrent glioblastoma (Table 6).[59,86-97] Unfortunately, the bevacizumab combination studies performed on a background of standard surgery, radiotherapy, and concurrent/adjuvant temozolomide therapy did not provide clear insight into new options for recurrent disease. Six studies in 357 evaluable patients, including one retrospective analysis, evaluated bevacizumab in combination with irinotecan.[59,88,89,92,94,96] In theory, the combination of irinotecan and bevacizumab might improve efficacy due to a synergy of antiangiogenic and cytostatic properties. Most trials employed a 10 mg/kg bevacizumab dosage regimen (range, 5-15 mg/kg) repeated every 2 weeks. Irinotecan was administered every 2 weeks in dosages of 125 without or 340 mg/m^2 with coadministration of enzyme-inducing antiepileptic drugs. Overall, the 6-month PFS rate was 30.0% to 50.3% with a median OS of 6.1 to 9.7 months. One phase 2 trial provided 6-month PFS rates stratified by patients experiencing first and second recurrences: 49% and 57.1%, respectively.[59] Overall, no additional benefit of irinotecan over that of bevacizumab alone became apparent.

Another small phase 2 study (32 evaluable patients) tested the triple combination of bevacizumab, irinotecan, and cetuximab in patients experiencing a first relapse within 6 months of standard temozolomide therapy.[87] Complete and partial responses were achieved in 2/32

(6.3%) and 9/32 (28.1%) patients, respectively. The 6-month PFS rate was 33% with a median OS of 7.0 months. A total of 4 and 20 grade 3/4 hematologic and nonhematologic events were reported, respectively. The addition of cetuximab was relatively well tolerated, except for skin toxicity; however, overall efficacy did not appear to be enhanced with the addition of cetuximab to the bevacizumab and irinotecan combination regimen.

A retrospective analysis of triple combination therapy with bevacizumab, carboplatin, and etoposide included 6 patients treated at first (n = 2), second (n = 2), third (n = 1), or fourth (n = 1) recurrences.[86] All patients had received focal radiation therapy and concurrent and adjuvant temozolomide following initial diagnosis and surgical intervention. Following 2 to 3 cycles of the triple drug regimen, a partial response was achieved in 5/6 patients. The combination was generally well tolerated. However, only marginally improved survival end points were reported: 22% 6-month PFS rate and a median OS of 6.9 months. Recurrent tumor was found in 4/5 patients with an initial response.

Reardon and colleagues evaluated the efficacy of bevacizumab and etoposide among 27 patients with primarily first recurrences (n = 14).[91] A complete and partial response was observed in one and 6 patients, respectively. A 44.4% 6-month PFS rate and a median OS of 10.2 months were reported. Notably, high VEGF expression (>30% of cells; $P = 0.006$) detected by immunochemistry of archival, paraffin-embedded tumor sections was associated with a better PFS.

Sathornsumete and colleagues evaluated bevacizumab in combination with erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor, in a phase 2 study of 24 evaluable temozolomide-pretreated patients with recurrent glioblastoma.[90] The 6-month PFS rate and median OS were 29.2% and 10.3 months, respectively. Survival end points of patients treated >3

months post radiotherapy were similar to the overall population. In summary, this combination did not appear to provide improved survival benefits when compared with historical bevacizumab-containing regimens.

Bevacizumab was also studied in combination with hypofractionated stereotactic radiotherapy in a small pilot study.[98] The investigators hypothesized that bevacizumab might increase tumor sensitivity to radiotherapy via depletion of VEGF and reduction of its signaling. Among 20 evaluable patients with recurrent glioblastoma (median number of recurrences, 1), the 6-month PFS rate was 65% with a median OS of 12.5 months. Most patients had reirradiation in the same local region as originally treated. The combination was well tolerated with no unusual adverse events in this heavily pretreated population. Notably, this bevacizumab/radiotherapy combination was superior to findings from another study, where patients received reirradiation alone for recurrent disease.[99] This approach deserves further consideration for the minority of eligible patients.

Significance of *MGMT* Promotor Methylation Status in Recurrent Disease

MGMT, a cellular DNA repair protein, rapidly reverses methylation via its suicide inactivation, thereby minimizing mutations and replication errors and restoring normal cellular homeostasis.[100-102] Patients whose tumors have a methylated *MGMT* promoter, which probably results in lower MGMT protein levels, are more likely to respond to alkylating agents because the tumor cells are unable to repair chemotherapy-induced DNA damage.[103,104]

A direct, real-time methylation-specific PCR assay (MSP) is the current preferred method for determining the *MGMT* status.[105] The MSP assay detects CpG island methylation with high sensitivity and specificity in clinical samples and has been shown to be highly reproducible

compared with the clinically validated nested, gel-based assay.[5] At present, methylation assays remain the most reliable technique for assessing the prognostic impact of MGMT status.

Two important issues are evident regarding the *MGMT* status and recurrent glioblastoma: 1) whether changes in status occur between primary and recurrent glioblastoma and 2) whether positive status correlates with better outcome following recurrent disease.

Among 80 patients with recurrent glioblastoma, including 64 patients treated with radiotherapy and temozolomide after the first operation, changes in *MGMT* promoter methylation status using the MSP technique were rarely found.[106] Overall, 88.8% of patients showed an unchanged methylation status upon comparison of individual pairs of primary and recurrent glioblastomas. Seven patients (8.8%) showed loss or reduction of *MGMT* promoter methylation at recurrence. These findings suggest that *MGMT* retesting is unnecessary in patients with recurrence. Notably, the prognostic significance of the *MGMT* status was upheld for patients experiencing a recurrence. Significantly longer PFS and OS were found in patients with *MGMT* promoter-methylated tumors and correlated with favorable outcome under salvage alkylating chemotherapy.

A preliminary report found that patients with a methylated *MGMT* status had a higher median PFS of 7.4 months compared with an unmethylated status (2 months; $P = 0.08$).[53] Median OS was also significantly higher in patients with *MGMT*-methylated tumors (16 months vs 11.5 months; $P = 0.05$). Additionally, the probability of achieving a radiographic response (PR/SD) was higher in patients with *MGMT* promoter methylation ($P = 0.03$).

Among 24 patients with *MGMT* status determined by MSP, the disease control rate was greater in patients with tumors with a methylated (3/7; 42%) as opposed to an unmethylated (6/17; 35%) *MGMT* promoter.[33] A trend toward a prolonged 6-month PFS was also observed;

however, neither end point achieved statistical significance.

In a prospective report conducted from 2005 to 2007, which included 22 patients who had recurrent glioblastoma and who underwent surgery with carmustine wafer implantation, methylated *MGMT* status determined by MSP was correlated with better outcome.[107] Median PFS and OS rates in methylated patients were 8.9 and 14.2 months, respectively, versus 2.7 and 9.2 months in unmethylated patients ($P \leq 0.031$ for both end points). Notably, this small study also found that *MGMT* status did not appear to change between primary and recurrent tumors.

In contrast, several other studies describe the absence of significant PFS and OS differences with regard to the methylation status of the *MGMT* promoter in patients with recurrent disease.[43,47,52,84,108] In most of these studies, *MGMT* promoter methylation status was analyzed using MSP. The absence of a correlation between *MGMT* promotor status and positive outcome in these studies may be attributed to the overall poor prognosis at glioblastoma recurrence, a small sample size, or the lack of a true association between *MGMT* status and outcome at time of recurrence. In the RESCUE study, 50/120 patients had tissue available for *MGMT* analysis and 42% were methylated. The use of a continuous daily temozolomide regimen at first recurrence in the glioblastoma groups was associated with similar PFS at 6 months, time to progression, and OS in both methylated and unmethylated patients.[51] It is unclear if the absence of correlation in this trial relates to the clinical factors listed previously or may be in part an effect of MGMT depletion with the protracted treatment schedule. Further validation studies in larger patient populations are needed to confirm that *MGMT* status is useful in predicting response to therapy and prognosis in patients with recurrent/progressive disease. The DIRECTOR trial[57] will provide prospective data that may clarify this issue. Yet, the impact of *MGMT* status, if any, is likely to be small and in the range of a few months, as can be estimated

from the studies that reported any effect at all.

Standard of care recommendations for recurrent/progressive glioblastoma

Appropriate management outside of clinical trials requires individualization based on patient age, performance status, histology, extent of initial resection, type of and response to initial therapy, time since diagnosis, and whether the recurrence is local or diffuse.[109] Repeat surgery, reirradiation, and second-line mono- or combination therapy are all primarily directed at reducing tumor burden and extension. All therapies aim to improve neurologic symptoms, e.g., headaches or seizures, reduce the need for certain medications or lower total daily doses, e.g., corticosteroids or antiepileptic drugs, and prevent thromboembolic complications.

Predicting response to subsequent therapy in patients with recurrent disease remains difficult because of the biological complexity of glioblastoma[110] as well as numerous other patient-specific factors. The role of *MGMT* as a prognostic or predictive marker following relapse remains ambiguous. Most contemporary clinical trials include a translational research program, but no biomarkers of practical use have yet been established.[111]

The 6-month PFS rate and median OS remain the most useful and accessible end points for monitoring outcomes following chemotherapy. OS is commonly considered the "gold standard" end point because it can be measured objectively and has clinical significance.[112] However, interpretation of OS can be affected by subsequent salvage therapy. PFS relies on a standardized method that defines tumor progression, but its determination can be challenging.[15] Currently the use of both median OS and 6-month PFS remain the best end points available for assessing therapeutic outcome in patients with recurrent disease. However, earlier PFS assessments also have been shown to similarly predict survival time and may become new end

points in future clinical trials.[22]

Despite advanced imaging techniques, detecting tumor progression remains a clinical challenge in patients with glioblastoma because of the complexities of pseudoprogression and radionecrosis.[113] An international expert panel has recently recommended that PFS should be correlated with OS end points and ideally validated with the RANO criteria.[112]

Which patients are most likely to benefit from dose-dense (metronomic) temozolomide therapy? The theoretical benefit of the metronomic approach is that it may deplete MGMT, leading to restoration of temozolomide sensitivity in *MGMT*-methylated tumors and/or may limit endothelial cell recovery and upregulate thrombospondin 1, leading to a sustained antiangiogenic effect.[109,114] Two randomized trials, the RTOG 0525 trial for newly diagnosed patients[6] and the BR12 trial for recurrent malignant glioma patients,[55] failed to demonstrate superiority of dose-intensified temozolomide over conventional temozolomide. Yet, neither of these trials can answer the question whether dose-intensified temozolomide is a suitable option for patients failing standard temozolomide because this setting was not examined in either trial. Many dose-dense rechallenge schedules have been evaluated as discussed above, e.g., 7/14 days, 21/28 days, 6/8 weeks, or continuously daily. The RESCUE study provides a glimpse of possible subpopulations that might benefit the most from metronomic temozolomide therapy. Patients who progressed after concomitant temozolomide/radiotherapy during the 6-month course of adjuvant temozolomide as well as patients who progressed later than 2 months after completing adjuvant temozolomide therapy appeared to benefit more from continuous temozolomide therapy (50 mg/m^2/d for 1 year) when compared with those who progressed while undergoing an extended adjuvant treatment of >6 months.[51] Larger trials with prospective stratification of

patients by extent of prior temozolomide therapy would be needed to fully answer the question which patients are best treated by temozolomide rechallenge.

Which temozolomide schedule provides the best outcome? Despite the increased number of prospective clinical trials conducted over the past 5 years, available data suggest that 6-month PFS and OS outcomes are similar among the various extended temozolomide dose-dense regimens used in patients with recurrent disease. However, most studies were small phase 2 trials and often included heterogeneous populations, e.g., varying types of prior chemotherapy, number of previous relapses, making it difficult to truly compare dose-dense regimens within or between trials. It may all come down to physician/patient preference and convenience unless the DIRECTOR trial[57] generates a clear signal for 1 of the 2 evaluated regimens.

Which temozolomide regimen has the least toxicity and is the best tolerated? In general, dose-dense temozolomide is associated with manageable toxicity in patients with recurrent glioblastoma previously treated with temozolomide. Wick and colleagues reported that among the various dose-dense schedules tested in phase 2 trials, each had a similar distribution of grade 1 to 4 toxicities.[54] However, compared with standard 5-of-28-day regimen, dose-dense regimens are associated with an increased incidence and severity of lymphocytopenia.[114] Available data from phase 2 trials suggests that lymphopenia occurs at a greater rate for patients receiving the "3-weeks-on, 1-week-off" regimen compared with the standard regimen. In general, at recurrence, starting at a moderate rechallenge dose may be advisable to identify the individual tolerance of the patients.

Which combination chemotherapies make the most sense? Currently, no single combination regimen has clearly emerged as a "favorite" for the treatment of recurrent or progressive glioblastoma. Temozolomide, in combination with cisplatin, fotemustine, interferon, sorafenib,

celecoxib, irinotecan, or procarbazine, lomustine, and vincristine, has not been demonstrated to be more effective than temozolomide alone (Table 5). Similarly, various bevacizumab-based combinations were not superior to historical data obtained with bevacizumab alone (Table 6).

Several other small studies have investigated the combination of protracted daily temozolomide (50 mg/m^2/d for 2-3 weeks) and biweekly bevacizumab for recurrent disease.[70,71] This combination provided similar efficacy compared with either agent alone, although heterogeneous patient populations, e.g., inclusion of patients who both responded and failed upfront therapy, may have confounded the findings.

Conclusions

A plethora of monotherapy and combination chemotherapy strategies have been evaluated in patients with recurrent or progressive glioblastoma. Despite some minor improvements in PFS, no obvious increase in survival has been associated with any particular regimen. Future clinical trials, which adopt the revised Macdonald criteria (RANO), may provide new clues as to which agent or combination is most beneficial. Despite definitive data, standard of care guidance for managing patients with recurrent or progressive glioblastoma is evolving. Further insight regarding which patients should undergo a second resection or radiotherapy procedure, how to best use temozolomide and bevacizumab therapy, and the value of *MGMT* status assessment in the recurrent setting is forthcoming.

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References

1. Central Brain Tumor Registry of the United States. CBTRUS statistical report: CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2004-2007. www.cbtrus.org. Accessed June 28, 2012.
2. Preusser M, de Ribaupierre S, Wohrer A, et al. Current concepts and management of glioblastoma. *Ann Neurol.* 2011;70(1):9-21.
3. Johnson DR, O'Neill BP. Glioblastoma survival in the United States before and during the temozolomide era. *J Neurooncol.* 2012;107(2):359-364.
4. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 2005;352(10):987-996.
5. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med.* 2005;352(10):997-1003.
6. Gilbert MR, Wang M, Aldape KD, et al. RTOG 0525: A randomized phase III trial comparing standard adjuvant temozolomide (TMZ) with a dosedense (dd) schedule in newly diagnosed glioblastoma (GBM). *J Clin Oncol.* 2011;29(suppl):2006.
7. National Comprehensive Cancer Network. NCCN guidelines: central nervous system cancers. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed June 28, 2012.
8. Macdonald DR, Cascino TL, Schold SC, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol.* 1990;8(7):1277-1280.
9. Brandsma D, Stalpers L, Taal W, Sminia P, van den Bent MJ. Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. *Lancet Oncol.* 2008;9(5):453-461.

10. Brandes AA, Franceschi E, Tosoni A, et al. MGMT promoter methylation status can predict the incidence and outcome of pseudoprogression after concomitant radiochemotherapy in newly diagnosed glioblastoma patients. *J Clin Oncol.* 2008;26(13):2192-2197.

11. Taal W, Brandsma D, de Bruin HG, et al. Incidence of early pseudo-progression in a cohort of malignant glioma patients treated with chemoirradiation with temozolomide. *Cancer.* 2008;113(2):405-410.

12. Oh J, Sahgal A, Sanghera P, et al. Glioblastoma: patterns of recurrence and efficacy of salvage treatments. *Can J Neurol Sci.* 2011;38(4):621-625.

13. Wick W, Stupp R, Beule A-C, et al. A novel tool to analyse MRI recurrence patterns in glioblastoma. *Neuro Oncol.* 2008;10(6):1019-1024.

14. Lutz K, Radbruch A, Wiestler B, Baumer P, Wick W, Bendszus M. Neuroradiological response criteria for high-grade gliomas. *Clin Neuroradiol.* 2011;21(4):199-205.

15. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol.* 2010;28(11):1963-1972.

16. Barbagallo GM, Jenkinson MD, Brodbelt AR. 'Recurrent' glioblastoma multiforme, when should we reoperate? *Br J Neurosurg.* 2008;22(3):452-455.

17. Park JK, Hodges T, Arko L, et al. Scale to predict survival after surgery for recurrent glioblastoma multiforme. *J Clin Oncol.* 2010;28(24):3838-3843.

18. Brem H, Piantadosi S, Burger PC, et al. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for

recurrent gliomas. The Polymer-brain Tumor Treatment Group. *Lancet.* 1995;345(8956):1008-1012.

19. Dhermain F, de Crevoisier R, Parker F, et al. [Role of radiotherapy in recurrent gliomas]. *Bull Cancer.* 2004;91(11):883-889.

20. Combs SE, Debus J, Schulz-Ertner D. Radiotherapeutic alternatives for previously irradiated recurrent gliomas. *BMC Cancer.* 2007;7:167.

21. Bendszus M, Debus J, Wick W, et al. APG101_CD_002: A phase II, randomized, open-label, multicenter study of weekly APG101 plus reirradiation versus reirradiation in the treatment of patients with recurrent glioblastoma. *J Clin Oncol.* 2012;30(suppl). Abstract 2034.

22. Lamborn KR, Yung WK, Chang SM, et al. Progression-free survival: an important end point in evaluating therapy for recurrent high-grade gliomas. *Neuro Oncol.* 2008;10(2):162-170.

23. Yung WK, Albright RE, Olson J, et al. A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. *Br J Cancer.* 2000;83(5):588-593.

24. Brada M, Hoang-Xuan K, Rampling R, et al. Multicenter phase II trial of temozolomide in patients with glioblastoma multiforme at first relapse. *Ann Oncol.* 2001;12(2):259-266.

25. van den Bent MJ, Brandes AA, Rampling R, et al. Randomized phase II trial of erlotinib versus temozolomide or carmustine in recurrent glioblastoma: EORTC brain tumor group study 26034. *J Clin Oncol.* 2009;27(8):1268-1274.

26. Brandes AA, Tosoni A, Amista P, et al. How effective is BCNU in recurrent glioblastoma in the modern era? A phase II trial. *Neurology.* 2004;63(7):1281-1284.

27. Reithmeier T, Graf E, Piroth T, Trippel M, Pinsker MO, Nikkhah G. BCNU for recurrent glioblastoma multiforme: efficacy, toxicity and prognostic factors. *BMC Cancer.* 2010;10:30.

28. Wick W, Puduvalli VK, Chamberlain MC, et al. Phase III study of enzastaurin compared with lomustine in the treatment of recurrent intracranial glioblastoma. *J Clin Oncol.* 2010;28(7):1168-1174.

29. Ahluwalia MS. 2010 Society for Neuro-Oncology Annual Meeting: a report of selected studies. *Expert Rev Anticancer Ther.* 2011;11(2):161-163.

30. Batchelor T, Mulholland P, Neyns B, et al. The efficacy of cediranib as monotherapy and in combination with lomustine compared to lomustine alone in patients with recurrent glioblastoma: a phase III randomized trial [abstract/slide set]. *Neuro Oncol.* 2010;12 (Suppl 4):75.

31. Happold C, Roth P, Wick W, et al. ACNU-based chemotherapy for recurrent glioma in the temozolomide era. *J Neurooncol.* 2009;92(1):45-48.

32. Balana C, Villa S, Teixidor P. Evolution of care for patients with relapsed glioblastoma. *Expert Rev Anticancer Ther.* 2011;11(11):1719-1729.

33. Addeo R, Caraglia M, De Santi MS, et al. A new schedule of fotemustine in temozolomide-pretreated patients with relapsing glioblastoma. *J Neurooncol.* 2011;102(3):417-424.

34. Brandes AA, Tosoni A, Franceschi E, et al. Fotemustine as second-line treatment for recurrent or progressive glioblastoma after concomitant and/or adjuvant temozolomide: a phase II trial of Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO). *Cancer Chemother Pharmacol.* 2009;64(4):769-775.

35. Scoccianti S, Detti B, Sardaro A, et al. Second-line chemotherapy with fotemustine in temozolomide-pretreated patients with relapsing glioblastoma: a single institution experience. *Anticancer Drugs.* 2008;19(6):613-620.

36. Fabrini MG, Silvano G, Lolli I, et al. A multi-institutional phase II study on second-line Fotemustine chemotherapy in recurrent glioblastoma. *J Neurooncol.* 2009;92(1):79-86.

37. Schmidt F, Fischer J, Herrlinger U, Dietz K, Dichgans J, Weller M. PCV chemotherapy for recurrent glioblastoma. *Neurology.* 2006;66(4):587-589.

38. Kappelle AC, Postma TJ, Taphoorn MJ, et al. PCV chemotherapy for recurrent glioblastoma multiforme. *Neurology.* 2001;56(1):118-120.

39. Brandes AA, Ermani M, Basso U, et al. Temozolomide as a second-line systemic regimen in recurrent high-grade glioma: a phase II study. *Ann Oncol.* 2001;12(2):255-257.

40. Brandes AA, Ermani M, Basso U, et al. Temozolomide in patients with glioblastoma at second relapse after first line nitrosourea-procarbazine failure: a phase II study. *Oncology.* 2002;63(1):38-41.

41. Khan RB, Raizer JJ, Malkin MG, Bazylewicz KA, Abrey LE. A phase II study of extended low-dose temozolomide in recurrent malignant gliomas. *Neuro Oncol.* 2002;4(1):39-43.

42. Chan DT, Poon WS, Chan YL, Ng HK. Temozolomide in the treatment of recurrent malignant glioma in Chinese patients. *Hong Kong Med J.* 2005;11(6):452-456.

43. Brandes AA, Tosoni A, Cavallo G, et al. Temozolomide 3 weeks on and 1 week off as first-line therapy for recurrent glioblastoma: phase II study from gruppo italiano cooperativo di neuro-oncologia (GICNO). *Br J Cancer.* 2006;95(9):1155-1160.

44. Nagane M, Kobayashi K, Ohnishi A, Shimizu S, Shiokawa Y. Prognostic significance of O6-methylguanine-DNA methyltransferase protein expression in patients with recurrent glioblastoma treated with temozolomide. *Jpn J Clin Oncol.* 2007;37(12):897-906.

45. Balmaceda C, Peereboom D, Pannullo S, et al. Multi-institutional phase II study of temozolomide administered twice daily in the treatment of recurrent high-grade gliomas. *Cancer.* 2008;112(5):1139-1146.

46. Wick W, Steinbach JP, Kuker WM, Dichgans J, Bamberg M, Weller M. One week on/one week off: a novel active regimen of temozolomide for recurrent glioblastoma. *Neurology.* 2004;62(11):2113-2115.

47. Wick A, Felsberg J, Steinbach JP, et al. Efficacy and tolerability of temozolomide in an alternating weekly regimen in patients with recurrent glioma. *J Clin Oncol.* 2007;25(22):3357-3361.

48. Franceschi E, Omuro AM, Lassman AB, Demopoulos A, Nolan C, Abrey LE. Salvage temozolomide for prior temozolomide responders. *Cancer.* 2005;104(11):2473-2476.

49. Kong DS, Lee JI, Kim WS, et al. A pilot study of metronomic temozolomide treatment in patients with recurrent temozolomide-refractory glioblastoma. *Oncol Rep.* 2006;16(5):1117-1121.

50. Berrocal A, Perez Segura P, Gil M, et al. Extended-schedule dose-dense temozolomide in refractory gliomas. *J Neurooncol.* 2010;96(3):417-422.

51. Perry JR, Belanger K, Mason WP, et al. Phase II trial of continuous dose-intense temozolomide in recurrent malignant glioma: RESCUE study. *J Clin Oncol.* 2010;28(12):2051-2057.

52. Kong DS, Lee JI, Kim JH, et al. Phase II trial of low-dose continuous (metronomic) treatment of temozolomide for recurrent glioblastoma. *Neuro Oncol.* 2010;12(3):289-296.

53. Hammond A, Norden AD, Lesser GJ, et al. Phase II study of dose-intense temozolomide in recurrent glioblastoma. *J Clin Oncol.* 2011;29:2038.

54. Wick A, Pascher C, Wick W, et al. Rechallenge with temozolomide in patients with recurrent gliomas. *J Neurol.* 2009;256(5):734-741.

55. Brada M, Stenning S, Gabe R, et al. Temozolomide versus procarbazine, lomustine, and vincristine in recurrent high-grade glioma. *J Clin Oncol.* 2010;28(30):4601-4608.

56. Weller M, Tabatabai G, Reifenberger G, et al. Dose-intensified rechallenge with temozolomide: one week on/one week off versus 3 weeks on/one week off in patients with progressive or recurrent glioblastoma. *J Clin Oncol.* 2010;28(15S). Abstract TPS154

57. Beal K, Abrey LE, Gutin PH. Antiangiogenic agents in the treatment of recurrent or newly diagnosed glioblastoma: analysis of single-agent and combined modality approaches. *Radiat Oncol.* 2011;6:2.

58. Seystahl K, Weller M. Is there a world beyond bevacizumab in targeting angiogenesis in glioblastoma? *Expert Opin Investig Drugs.* 2012;21(5):605-617.

59. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol.* 2009;27(28):4733-4740.

60. Kreisl TN, Kim L, Moore K, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. *J Clin Oncol.* 2009;27(5):740-745.

61. Raizer JJ, Grimm S, Chamberlain MC, et al. A phase 2 trial of single-agent bevacizumab given in an every-3-week schedule for patients with recurrent high-grade gliomas. *Cancer.* 2010;116(22):5297-5305.

62. Chamberlain MC, Johnston SK. Salvage therapy with single agent bevacizumab for recurrent glioblastoma. *J Neurooncol.* 2010;96(2):259-269.

63. Batchelor TT, Sorensen AG, di Tomaso E, et al. AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. *Cancer Cell.* 2007;11(1):83-95.

64. Batchelor TT, Duda DG, di Tomaso E, et al. Phase II study of cediranib, an oral pan-vascular endothelial growth factor receptor tyrosine kinase inhibitor, in patients with recurrent glioblastoma. *J Clin Oncol.* 2010;28(17):2817-2823.

65. de Groot JF, Lamborn KR, Chang SM, et al. Phase II study of aflibercept in recurrent malignant glioma: a North American Brain Tumor Consortium study. *J Clin Oncol.* 2011;29(19):2689-2695.

66. Wen PY, Prados M, Schiff D. Phase II study of XL184 (BMS 907351), an inhibitor of MET, VEGFR2, and RET, in patients (pts) with progressive glioblastoma (GB). *J Clin Oncol.* 2010;28(15 suppl). Abstract 2006.

67. Wen PY. American Society of Clinical Oncology 2010: report of selected studies from the CNS tumors section. *Expert Rev Anticancer Ther.* 2010;10(9):1367-1369.

68. Reardon DA, Fink KL, Mikkelsen T, et al. Randomized phase II study of cilengitide, an integrin-targeting arginine-glycine-aspartic acid peptide, in recurrent glioblastoma multiforme. *J Clin Oncol.* 2008;26(34):5610-5617.

69. Gilbert MR, Kuhn J, Lamborn KR, et al. Cilengitide in patients with recurrent glioblastoma: the results of NABTC 03-02, a phase II trial with measures of treatment delivery. *J Neurooncol.* 2012;106(1):147-153.

70. Verhoeff JJ, Lavini C, van Linde ME, et al. Bevacizumab and dose-intense temozolomide in recurrent high-grade glioma. *Ann Oncol.* 2010;21(8):1723-1727.

71. Desjardins A, Reardon DA, Coan A, et al. Bevacizumab and daily temozolomide for recurrent glioblastoma. *Cancer.* 2012;118(5):1302-1312.

72. Chang SM, Prados MD, Yung WK, et al. Phase II study of neoadjuvant 1, 3-bis (2-chloroethyl)-1-nitrosourea and temozolomide for newly diagnosed anaplastic glioma: a North American Brain Tumor Consortium Trial. *Cancer.* 2004;100(8):1712-1716.

73. Gaviani P, Salmaggi A, Silvani A. Combined chemotherapy with temozolomide and fotemustine in recurrent glioblastoma patients. *J Neurooncol.* 2011;104(2):617-618.

74. Groves MD, Puduvalli VK, Gilbert MR, et al. Two phase II trials of temozolomide with interferon-alpha2b (pegylated and non-pegylated) in patients with recurrent glioblastoma multiforme. *Br J Cancer.* 2009;101(4):615-620.

75. Reardon DA, Vredenburgh JJ, Desjardins A, et al. Effect of CYP3A-inducing anti-epileptics on sorafenib exposure: results of a phase II study of sorafenib plus daily temozolomide in adults with recurrent glioblastoma. *J Neurooncol.* 2011;101(1):57-66.

76. Boiardi A, Silvani A, Eoli M, et al. Treatment of recurrent glioblastoma: can local delivery of mitoxantrone improve survival? *J Neurooncol.* 2008;88(1):105-113.

77. Reardon DA, Quinn JA, Rich JN, et al. Phase I trial of irinotecan plus temozolomide in adults with recurrent malignant glioma. *Cancer.* 2005;104(7):1478-1486.

78. Chua SL, Rosenthal MA, Wong SS, et al. Phase 2 study of temozolomide and Caelyx in patients with recurrent glioblastoma multiforme. *Neuro Oncol.* 2004;6(1):38-43.

79. Silvani A, Eoli M, Salmaggi A, et al. Phase II trial of cisplatin plus temozolomide, in recurrent and progressive malignant glioma patients. *J Neurooncol.* 2004;66(1-2):203-208.

80. Brandes AA, Basso U, Reni M, et al. First-line chemotherapy with cisplatin plus fractionated temozolomide in recurrent glioblastoma multiforme: a phase II study of the Gruppo Italiano Cooperativo di Neuro-Oncologia. *J Clin Oncol.* 2004;22(9):1598-1604.

81. Walbert T, Gilbert MR, Groves MD, et al. Combination of 6-thioguanine, capecitabine, and celecoxib with temozolomide or lomustine for recurrent high-grade glioma. *J Neurooncol.* 2011;102(2):273-280.

82. Eisenstat DD, Nabors LB, Mason W, et al. A phase II study of daily afatinib (BIBW 2992) with or without temozolomide (21/28 days) in the treatment of patients with recurrent glioblastoma. *J Clin Oncol.* 2011;29(suppl). Abstract 2010.

83. Quinn JA, Jiang SX, Reardon DA, et al. Phase II trial of temozolomide plus o6-benzylguanine in adults with recurrent, temozolomide-resistant malignant glioma. *J Clin Oncol.* 2009;27(8):1262-1267.

84. Stockhammer F, Misch M, Koch A, et al. Continuous low-dose temozolomide and celecoxib in recurrent glioblastoma. *J Neurooncol.* 2010;100(3):407-415.

85. Reardon DA, Desjardins A, Peters KB, et al. Phase 2 study of carboplatin, irinotecan, and bevacizumab for recurrent glioblastoma after progression on bevacizumab therapy. *Cancer.* 2011;117(23):5351-5358.

86. Francesconi AB, Dupre S, Matos M, et al. Carboplatin and etoposide combined with bevacizumab for the treatment of recurrent glioblastoma multiforme. *J Clin Neurosci.* 2010;17(8):970-974.

87. Hasselbalch B, Lassen U, Hansen S, et al. Cetuximab, bevacizumab, and irinotecan for patients with primary glioblastoma and progression after radiation therapy and temozolomide: a phase II trial. *Neuro Oncol.* 2010;12(5):508-516.

88. Narayana A, Kelly P, Golfinos J, et al. Antiangiogenic therapy using bevacizumab in recurrent high-grade glioma: impact on local control and patient survival. *J Neurosurg.* 2009;110(1):173-180.

89. Nghiemphu PL, Liu W, Lee Y, et al. Bevacizumab and chemotherapy for recurrent glioblastoma: a single-institution experience. *Neurology.* 2009;72(14):1217-1222.

90. Sathornsumetee S, Desjardins A, Vredenburgh JJ, et al. Phase II trial of bevacizumab and erlotinib in patients with recurrent malignant glioma. *Neuro Oncol.* 2010;12(12):1300-1310.

91. Reardon DA, Desjardins A, Vredenburgh JJ, et al. Metronomic chemotherapy with daily, oral etoposide plus bevacizumab for recurrent malignant glioma: a phase II study. *Br J Cancer.* 2009;101(12):1986-1994.

92. Vredenburgh JJ, Desjardins A, Herndon JE, 2nd, et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. *J Clin Oncol.* 2007;25(30):4722-4729.

93. Pope WB, Lai A, Nghiemphu P, Mischel P, Cloughesy TF. MRI in patients with high-grade gliomas treated with bevacizumab and chemotherapy. *Neurology.* 2006;66(8):1258-1260.

94. Vredenburgh JJ, Desjardins A, Herndon JE, 2nd, et al. Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. *Clin Cancer Res.* 2007;13(4):1253-1259.

95. Norden AD, Young GS, Setayesh K, et al. Bevacizumab for recurrent malignant gliomas: efficacy, toxicity, and patterns of recurrence. *Neurology.* 2008;70(10):779-787.

96. Gilbert MR, M. W, Aldape KD, et al. RTOG 0625: A phase II study of bevacizumab with irinotecan in recurrent glioblastoma (GBM) (abstract) *J Clin Oncol.* 2009;27 (Suppl)(15S):2011.

97. Stark-Vance V. Bevacizumab and CPT-11 in the treatment of relapsed malignant glioma. *Neuro Oncol.* 2005;7:369. Abstract 342.

98. Gutin PH, Iwamoto FM, Beal K, et al. Safety and efficacy of bevacizumab with hypofractionated stereotactic irradiation for recurrent malignant gliomas. *Int J Radiat Oncol Biol Phys.* 2009;75(1):156-163.

99. Vordermark D, Kolbl O, Ruprecht K, Vince GH, Bratengeier K, Flentje M. Hypofractionated stereotactic re-irradiation: treatment option in recurrent malignant glioma. *BMC Cancer.* 2005;5:55.

100. Casorelli I, Russo MT, Bignami M. Role of mismatch repair and MGMT in response to anticancer therapies. *Anticancer Agents Med Chem.* 2008;8(4):368-380.

101. Sharma S, Salehi F, Scheithauer BW, Rotondo F, Syro LV, Kovacs K. Role of MGMT in tumor development, progression, diagnosis, treatment and prognosis. *Anticancer Res.* 2009;29(10):3759-3768.

102. Weller M, Stupp R, Reifenberger G, et al. MGMT promoter methylation in malignant gliomas: ready for personalized medicine? *Nat Rev Neurol.* 2010;6(1):39-51.

103. Hegi ME, Liu L, Herman JG, et al. Correlation of O6-methylguanine methyltransferase (MGMT) promoter methylation with clinical outcomes in glioblastoma and clinical strategies to modulate MGMT activity. *J Clin Oncol.* 2008;26(25):4189-4199.

104. Esteller M, Garcia-Foncillas J, Andion E, et al. Inactivation of the DNA-repair gene MGMT and the clinical response of gliomas to alkylating agents. *N Engl J Med.* 2000;343(19):1350-1354.

105. Vlassenbroeck I, Califice S, Diserens AC, et al. Validation of real-time methylation-specific PCR to determine O6-methylguanine-DNA methyltransferase gene promoter methylation in glioma. *J Mol Diagn.* 2008;10(4):332-337.

106. Felsberg J, Thon N, Eigenbrod S, et al. Promoter methylation and expression of MGMT and the DNA mismatch repair genes MLH1, MSH2, MSH6 and PMS2 in paired primary and recurrent glioblastomas. *Int J Cancer.* 2011;129(3):659-670.

107. Metellus P, Coulibaly B, Nanni I, et al. Prognostic impact of O6-methylguanine-DNA methyltransferase silencing in patients with recurrent glioblastoma multiforme who undergo surgery and carmustine wafer implantation: a prospective patient cohort. *Cancer.* 2009;115(20):4783-4794.

108. Sadones J, Michotte A, Veld P, et al. MGMT promoter hypermethylation correlates with a survival benefit from temozolomide in patients with recurrent anaplastic astrocytoma but not glioblastoma. *Eur J Cancer.* 2009;45(1):146-153.

109. Easaw JC, Mason WP, Perry J, et al. Canadian recommendations for the treatment of recurrent or progressive glioblastoma multiforme. *Curr Oncol.* 2011;18(3):e126-e136.

110. Kesari S. Understanding glioblastoma tumor biology: the potential to improve current diagnosis and treatments. *Semin Oncol.* 2011;38(suppl 4):S2-10.

111. Weller M, Wick W, Hegi ME, Stupp R, Tabatabai G. Should biomarkers be used to design personalized medicine for the treatment of glioblastoma? *Future Oncol.* 2010;6(9):1407-1414.

112. Reardon DA, Galanis E, DeGroot JF, et al. Clinical trial end points for high-grade glioma: the evolving landscape. *Neuro Oncol.* 2011;13(3):353-361.

113. Mehta AI, Kanaly CW, Friedman AH, Bigner DD, Sampson JH. Monitoring radiographic brain tumor progression. *Toxins (Basel).* 2011;3(3):191-200.

114. Neyns B, Tosoni A, Hwu WJ, Reardon DA. Dose-dense temozolomide regimens: antitumor activity, toxicity, and immunomodulatory effects. *Cancer.* 2010;116(12):2868-2877.

115. Wen PY, Prados M, Schiff D, al. e. Phase II study of XL184 (BMS 907351), an inhibitor of MET, VEGFR2, and RET, in patients (pts) with progressive glioblastoma (GB). *J Clin Oncol.* 2010;28 (15 Suppl) Abstract 2006

Table 1. Neuroimaging and Glioblastoma: Macdonald vs RANO Criteria

	Macdonald	**RANO**
CR	Requires all of the following: • Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks • No new lesions • No corticosteroids • Stable or improved clinically	Requires all of the following: • Disappearance of all enhancing measurable and nonmeasurable disease sustained for a minimum of 4 weeks • Stable or improved FLAIR/T2 lesions • No new lesions • Stable or improved clinically • Patients cannot be receiving corticosteroids (physiologic replacement doses are acceptable)
PR	Requires all of the following: • ≥50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks • No new lesions • Stable or reduced corticosteroid dose • Stable or improved clinically	Requires all of the following: • 50% or greater decrease (compared with baseline) in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for a minimum of 4 weeks • No progression of nonmeasurable disease • No new lesions • Stable or improved FLAIR/T2 lesions

		• Stable or improved clinically • Corticosteroid dosage at the time of the scan should be no greater than the dosage at the time of the baseline scan
SD	Requires all of the following: • Does not qualify for CR, PR, or PD • Stable clinically	Requires all of the following: • Patient does not qualify for CR, PR, or progression • Stable FLAIR/T2 lesions on a corticosteroid dose no greater than at baseline • Stable clinically
PD	Defined by any of the following: • ≥25% increase in sum of the products of perpendicular diameters of enhancing lesions relative to best previous scan • Any new lesion • Clinical deterioration	Defined by any of the following: • 25% or greater increase in sum of the products of perpendicular diameters of all measurable enhancing lesions compared with the smallest tumor measurement obtained either at baseline or best response following the initiation of therapy, while on a stable or increasing dose of corticosteroids • Significant increase in FLAIR/T2

		lesions compared with baseline or best response following initiation of therapy, not caused by comorbid events (eg, radiation therapy, ischemic injury, seizures, postoperative changes, or other treatment effects), while on a stable or increasing dose of corticosteroids • New lesions • Clinical deterioration not attributable to other causes apart from the tumor (eg, seizures, medication side effects, complications of therapy, cerebrovascular events, infection) or decreases in corticosteroid dose • Failure to return for evaluation due to death or deteriorating condition • Clear progression of nonmeasurable disease

Abbreviations: CR, complete response; FLAIR, fluid-attenuated inversion recovery; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-Oncology; SD, stable disease. (Adapted from Lutz and Wen et al.)[14,15]

Table 2. Nitrosourea Trials in Recurrent or Progressive Glioblastoma[a]

Reference	Study Design/ Population	TMZ Pre-treatment	Nitrosourea Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WHO Grade 3/4 Toxicities (n)
Monotherapy									
Van den Bent MJ et al[25]	Phase 2, randomized Median age: 54 y	Some (not clearly specified)	BCNU 60 mg/m^2 on days 1-3 q8wk for max 5 cycles. *or* TMZ 200 mg/m^2 on days 1-5 q4wk in chemotherapy-naïve pts *or* 150 mg/m^2 on days 1-5 q4wk after prior adjuvant chemotherapy, with dose escalation to 200 mg/m^2 in absence of significant toxicity (only combined data [Cntrl] for BCNU and TMZ reported) *or* ERL 150 mg/d, with dose	BCNU: 29 TMZ: 27 (52 eval-uable in Cntrl) ERL: 54	*CR:* 0 *PR:* Cntrl: 5 vs ERL: 2 *SD:* Cntrl:18 vs ERL: 9	Cntrl: 24.1 vs ERL: 11.4	Cntrl: 2.4 vs ERL 1.8	Cntrl: 7.3 vs ERL 7.7	*Hematologic:* BCNU: 13 TMZ: 4 ERL: 1 *Nonhematologic:* BCNU: 8 TMZ: 4 ERL: 11

Reference	Study Design/ Population	TMZ Pre-treatment	Nitrosourea Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WHO Grade 3/4 Toxicities (n)
			escalation to 200 mg/d if no toxicity						
Brandes AA et al[26]	Phase 2 Median age: 49.7 y; Median KPS: 70	No	BCNU 80 mg/m^2 on days 1-3 q8wk for max 6 cycles	40	*CR:* 0 *PR:* 6 *SD:* 9 *PD:* NA	17.5	NA	7.53	*Hematologic:* NA *Nonhematologic:* 9
Reithmeier T et al[27]	Retrospective analysis Median age: 53 y; Median KPS: 70; 1st relapse: n=30; 2nd relapse: n=4; 4th relapse: n=1	24 (69%)	BCNU 80 mg/m^2 IV on days 1-3 q8wk for max 6 cycles	35	*CR:* 0 *PR:* 2 *SD:* 19 *PD:* 11	13	2.6	5.1	*Hematologic:* 10 *Nonhematologic:* 4
Wick W et al[28]	Phase 3 open-label, randomized 2:1 1st relapse: CCNU n=70; Enzastaurin	NA	CCNU 100-130 mg/m^2 on day 1 q6wk Enzastaurin 500 mg PO daily (1125-mg loading	92 174	*CR:* 0 *PR:* 4 *SD:* 33 *PD:* 38 *CR:* 0 *PR:* 5 *SD:* 67	19.0 11.1	1.6 1.5	7.1 6.1	*Hematologic:* 46 *Nonhematologic:* 3 *Hematologic:* 1 *Nonhematologic:*

Reference	Study Design/ Population	TMZ Pre-treatment	Nitrosourea Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WHO Grade 3/4 Toxicities (n)
	n=129 2nd relapse: CCNU n=21; Enzastaurin n=45		dose on day 1)		*PD:* 72				13 ($P < 0.007$ for hematologic toxicities)
Ahluwalia MS et al[29] Batchelor TT et al[30]	Phase 3, multicenter, double-blind, randomized 1:2:2 Median age: 54 y	Yes	CCNU 110 mg/m^2 q6wk + placebo *or* CED 30 mg/d *or* CED 20 mg/d + CCNU 110 mg/m^2 q6wk	65 131 129	*CR:* 0 *PR:* 5 *SD:* 23 *PD:* 23 *CR:* 1 *PR:* 17 *SD:* 76 *PD:* 10 *CR:* 2 *PR:* 19 *SD:* 67 *PD:* 19	24.5 16 34.5	2.73 3.1 4.2	9.8 8.0 9.4	*Hematologic:* 30 *Nonhematologic:* 16 *Hematologic:* 7 *Nonhematologic:* 66 *Hematologic:* 116 *Nonhematologic:* 57
Happold, CJ et al[31]	Retrospective analysis 2003-2008, after failed therapy with TMZ or recurrence	Yes	ACNU 72-90 mg/m^2/d IV in 6-wk cycles, alone or in combination	14 alone *or* 18 in com-binatio n	*CR:* 0[b] *PR:* 2[b] *SD:* 5[b] *PD:* NA[b]	20[b]	2.7[b]	6.7[b]	*Hematologic:* 16[b] *Nonhematologic:* 3[b]

Reference	Study Design/ Population	TMZ Pre-treatment	Nitrosourea Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WHO Grade 3/4 Toxicities (n)
Addeo R et al[33]	Phase 2, multicenter, nonrandomized, single-arm Median age: 52.8 y; Median KPS: 90; 1st relapse: 100%	Yes	FOT IV 80 mg/m^2 on days 1, 15, 30, 45, and 60 (induction), then 80 mg/m^2 q4wk (maintenance)	40	*CR:* 1 *PR:* 9 *SD:* 16 *PD:* 14	61	6.7	11.1	*Hematologic:* Induction: 5 Maintenance: 5 *Nonhematologic:* Induction: 0 Maintenance: 3
Brandes AA et al[34]	Phase 2, non-randomized, single-arm Median age: 51 y; Median KPS: 90	Yes	FOT 75-100 mg/m^2 for 3 weekly doses followed, after a 5-wk rest, by 100 mg/m^2 q3wk for ≤1 yr	43	*CR:* 0 *PR:* 3 *SD:* 15	20.9	1.7	6.0	*Hematologic:* Induction (100 mg/m^2): 24 Amended induction (75 mg/m^2): 19 Maintenance: 8 *Nonhematologic:* NA
Scoccianti S et al[35]	Phase 2, multicenter, single-arm Median age: 56 y; Median KPS:	Yes	FOT IV 100 mg/m^2 qwk for 3 consecutive wks (induction), then q3wk (maintenance)	27	*CR:* 0 *PR:* 8 *SD:* 5 *PD:* 14	48.2	5.7	9.1	*Hematologic:* 4 pts *Nonhematologic:* 0

Reference	Study Design/ Population	TMZ Pre-treatment	Nitrosourea Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WHO Grade 3/4 Toxicities (n)
	80; 1st recurrence: 100%								
Fabrini MG et al[36]	Phase 2, multicenter, prospective, open-label, non-comparative Median age: 56.8 y; Median KPS: 90	Yes	FOT 100 mg/m^2 IV on days 1, 8, and 15, followed by 4- to 6-wk rest period (induction). In nonprogressive pts, FOT 100 mg/m^2 IV q3wk (maintenance)	50	*CR:* 1 *PR:* 8 *SD:* 22 *PD:* 19	52	6.1	8.1	*Hematologic:* 7 pts *Nonhematologic:* 0
Combination Regimens									
Kappelle AC et al[38]	Multicenter retrospective, 1994-1998 Median age: 46 y; Median KPS: 80	Only 4 pts	Standard or intensified PRO, CCNU, and VIN	63	*CR:* 3 *PR:* 8 *SD:* 25	29	NA	7.7	*Hematologic:* NA *Nonhematologic:* NA
Schmidt F et al.[37]	Retro-spective chart review, 1994-2003 Median age:	Only 12 pts	PRO 60 mg/m^2 PO days 8-21, CCNU 110 mg/m^2 PO day 1, VIN 1.4 mg/m^2 [max 2 mg] IV	86	*CR:* 0 *PR:* 3 *SD:* 45 *PD:* 18	38.4	4.0	7.8	*Hematologic:* 30 pts *Nonhematologic:* 0

Reference	Study Design/ Population	TMZ Pre-treatment	Nitrosourea Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WHO Grade 3/4 Toxicities (n)
	49 y; 1st relapse: 100%		days 8 and 29; given in 8-wk cycles						

Abbreviations: ACNU, nimustine; BCNU, carmustine; CCNU, lomustine; CED, cediranib; Cntrl, control arm; CR, complete response; ERL, erlotinib; FOT, fotemustine; IV, intravenous; max, maximum; KPS, Karnofsky Performance Score; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; PD, progressive disease; PFS, progression-free survival; PR, partial response; PRO, procarbazine; pts, patients; SD, stable disease; TMZ, temozolomide; VIN, vincristine.
For the most part, only glioblastoma data are presented in the table. We have reported enrollment numbers for different patient populations only when all data in a paper are presented for combined patient populations.
* The disease progression-free survival and the overall survival were calculated from beginning of retreatment.
[a] All data presented for glioblastoma patients only.
[b] Data for ACNU alone were not available; the numbers listed represent responses for all patients (ACNU alone and in combination).

Table 3. Temozolomide Monotherapy Trials in Recurrent or Progressive Glioblastoma[a]

Ref	Study Design/ Population	TMZ Pretreat-ment	TMZ Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WH Grade 3/4 Toxicities (n)
Temozolomide-Naïve Population									
Brada M et al[24]	Phase 2, open-label, uncontrolled TMZ at 1st relapse Median age: 54 y; Median time to 1st relapse: 8.1 mo	No (40% of pts had prior nitrosourea-containing chemo-therapy)	Chemotherapy-naïve pts: 200 mg/m^2/d PO for 1st 5 days of 28-day cycle Pts with previous nitrosourea-containing adjuvant chemotherapy: 150 mg/m^2/d for 1st 5 days of 28-day cycle	126	*CR:* 2 *PR:* 8 *SD:* 57	18	2.1	5.4	*Hematologic:* 30 *Nonhematologic:* 30
Brandes AA et al[39]	Phase 2 2nd relapse	No (previous PCV)	150 mg/m^2/d for 5 days q28d	22	*CR:* 2 *PR:* 3 *SD:* 4	31.8		7.6	*Hematologic:* 4 *Nonhematologic:* 2
Brandes AA et al[40]	Phase 2 Mean age: 48.4 y; Median KPS: 80	No (previous PCV)	150 mg/m^2/d for 5 days q28d	42	*CR:* 2 *PR:* 6 *SD:* 9 *PD:* NA	24	NA	7.0	*Hematologic:* 1 *Nonhematologic:* 0

Ref	Study Design/ Population	TMZ Pretreat-ment	TMZ Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WH Grade 3/4 Toxicities (n)
	2nd relapse								
Khan RB et al[41]	Phase 2, prospective, extended low-dose, single-center	No	75 mg/m^2/d for 42 days q70d	28	*CR:* 0 *PR:* 0 *SD:* 11 *PD:* 17	19	2.3	7.7	*Hematologic:* 8 *Nonhematologic:* 0
Wick W et al[46]	Phase 2, nonrandomized, prospective	No	150 mg/m^2 on days 1-7 and days 15-21 of 28-day cycles for max 12 cycles	21	*CR:* 0 *PR:* 2 *SD:* 17 *PD:* 2	48	4.9	NA	*Hematologic:* 10 *Nonhematologic:* 7
Chan DT et al[42]	Prospective, open-label, compassionate use in Chinese pts	No	200 mg/m^2/d for 5 days q28d for 4 cycles	13	NA	21.0	NA	NA	*Hematologic:* 0 *Nonhematologic:* 0
Brandes AA et al[43]	Phase 2 Median age: 57 y; Median KPS: 90	No	75 mg/m^2/d for 21 days q28d	33	*CR:* 1 *PR:* 2 *SD:* 17	30.3	3.8	9.3	*Hematologic:* 14 *Nonhematologic:* 4
Nagane M et al[44]	Prospective, open-label Mean age: 48.2 y; Median KPS:	No (89.5% had previous nitrosourea-based therapy)	150-200 mg/m^2/d for 5 days q28d	19	*CR:* 1 *PR:* 3 *SD:* 6 *PD:* 7	22.2	2.2	9.9	*Hematologic:* 5 *Nonhematologic:* 9

Ref	Study Design/ Population	TMZ Pretreat-ment	TMZ Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WH Grade 3/4 Toxicities (n)
	70								
Balmaceda C et al[45]	Phase 2, single-arm, multicenter Median age: 43 y; 1st relapse: n=48; ≥2 relapses: n=20	No (previous non-nitrosourea: n=7; nitrosourea: n=33; none: n=28)	200 mg/m^2 initial dose, then 9 consecutive doses at 90 mg/m^2 q12h for 28 days; increased to 100 mg/m^2 q12h in absence of toxicity	68	*CR:* 3 *PR:* 18 *SD:* 22 *PD:* 19	35	4.0	9.0	*Hematologic:* NA *Nonhematologic:* NA
Temozolomide-Pretreated Population									
Francesc hi E et al[48]	Retrospective analysis	Yes	150-200 mg/m^2/d for 5 days, q28d in 13 pts, 25 mg/m^2/d continuously in 1 pt	9	*CR:* 2 *PR:* 2 *SD:* 2 *PD:* 3	NA	7.0	12+	*Hematologic:* 1 *Nonhematologic:* 0
Kong DS et al[49]	Pilot study, metronomic Median age: 48.3 y	Yes	40 mg/m^2/d (3 mo)	12	*CR:* 0 *PR:* 2 *SD:* 5 *PD:* 5	58.3	6.0	11	*Hematologic:* 0 *Nonhematologic:* 0
Wick W et al[47]	Prospective, non-randomized:	9/64 pts had received TMZ	150 mg/m^2 on days 1-7 and days 15-21	64	NA	43.8	5.5	NA	NA

Ref	Study Design/ Population	TMZ Pretreat-ment	TMZ Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WH Grade 3/4 Toxicities (n)
	alternating weekly regimen Median age: 51 y	(+ CCNU)	q28d (1-wk on, 1-wk off)						
Wick W et al[54b]	Retrospective analysis, 3 centers, 2000-2007 Median age: 52 y *2 cohorts:* TMZ escalation with progression during TMZ vs TMZ rechallenge after stable disease and disease-free interval	Yes	75 mg/m^2/d (days 1-42 during radiotherapy), plus 150-200 mg/m^2/d for 5 days q28d *or* 150-200 mg/m^2/d for 5 days q28d *or* 150 mg/m^2/d for 1-wk on, 1-wk off *or* 75 mg/m^2/d for 21 days q28d *or*	47	NA	27.7 (pro-gressive cohort 26.3 vs stable cohort 28.6%)		5.8 (pro-gressive cohort 6.6 vs stable cohort 5.3)	*Hematologic:* 22 *Nonhematologic:* 10

Ref	Study Design/ Population	TMZ Pretreat-ment	TMZ Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WH Grade 3/4 Toxicities (n)
			40 mg/d continuous[c]						
Berrocal A et al[50]	Phase 2, multicenter	Yes	85 mg/m^2 for 21 days q28d	GB: 27 AA: 15 Misc: 5	*CR:* 0 *PR:* 2 *SD:* 15[a] *PD:* 30[a]	0	NA	5.1[a]	NA
Perry JR et al[51]	Phase 2, continuous dose-intense (RESCUE study), multicenter Pts prospectively divided into 3 groups (early, extended, and rechallenge) per timing of progression during adjuvant therapy	Yes	50 mg/m^2/d continuous for max 1 yr or progression	91	NA	23.9 (early 27.3; extended 7.4; re-challenge 35.7)	NA (early 3.6; extended 1.8; re-challenge 3.7)	9.3	NA
Kong DS	Phase 2, low-	Yes	40-50	38	*CR:* 0	32.5	4.0	9.6	*Hematologic:*

Ref	Study Design/ Population	TMZ Pretreat-ment	TMZ Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WH Grade 3/4 Toxicities (n)
et al[52]	dose, continuous (metronomic) Median age: 51 y		mg/m^2/d		*PR:* 2 *SD:* 21				4 *Nonhematologic:* 0
Hammond A et al[53] (prelim results only)	Phase 2, dose-intense, single-arm 1st recurrence Median age: 57 y; Median KPS: 90	Yes	75-100 mg/m^2/d for 21 days q28d	47	*CR:* 0 *PR:* 6 *SD:* 18	23	2.3	13	*Hematologic:* 7 *Nonhematologic:* NA
Randomized Studies									
Yung WK et al[23]	Phase 2, randomized, multicenter, open-label 1st relapse: 100%; Median age: 51-52 y	No (65-68% of pts received prior nitrosourea)	TMZ 150-200 mg/m^2/d for 5 days q28d *or* Procarbazine 150 mg/m^2/d (or 125 mg/m^2/d if prior chemo-therapy) PO for 28 days, repeated q56d	112 113	*CR:* 0 *PR:* 6 *SD:* 45 *CR:* 0 *PR:* 6 *SD:* 31	21 8	2.9 1.9	NA	*Hematologic:* 14 *Nonhematologic:* 12 *Hematologic:* 9 *Nonhematologic:* 17

Ref	Study Design/ Population	TMZ Pretreat-ment	TMZ Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WH Grade 3/4 Toxicities (n)
Brada M et al[55]	Prospective, randomized 1st progression: 100%	No (chemo-therapy-naïve)	TMZ 200 mg/m^2 for 5 days *or* TMZ 100 mg/m^2 for 21 days *or* PCV	GB: 72 AA: 15 GB: 66 AA: 15 GB: 139 AA: 23	NA	NA	5.0[a] 4.2[a] 3.6[a]	8.5[a] 6.6[a] 6.7[a]	*Hematologic:* 38[a] *Nonhematologic:* 37[a] *Hematologic:* 28[a] *Nonhematologic:* 38[a] *Hematologic:* 57[a] *Nonhematologic:* 64[a]

Abbreviations: AA, anaplastic astrocytoma; CR, complete response; GB, glioblastoma; KPS, Karnofsky Performance Score; mOS, median overall survival; mPFS, median progression-free survival; PCV, procarbazine, CCNU, and vincristine; PD, progressive disease; PFS, progression-free survival; PR, partial response; pts, patients; SD, stable disease; TMZ, temozolomide.
For the most part, only glioblastoma data are presented in the table. We have reported enrollment numbers for different patient populations only when all data in a paper are presented for combined patient populations.
*The disease progression-free survival and the overall survival were calculated from beginning of retreatment with temozolomide.
[a] Data presented for glioblastoma patients only except for Berrocal 2010 study,[50] where 27 patients had glioblastoma, 15 had anaplastic astrocytoma, and 5 had miscellaneous brain tumors, and Brada 2010 study,[55] where 277 patients had glioblastoma, 53 had anaplastic astrocytoma, and 20 had miscellaneous brain tumors.
[b] Retrospective study.
[c] 11patients also received 13-cis-retinoic acid or pegylated liposomal doxorubicin.

Table 4. Bevacizumab Monotherapy and Miscellaneous Antiangiogenic Trials in Recurrent or Progressive Glioblastoma[a]

Reference	Study Design/ Population	TMZ Pre-treatment	Antiangiogenic Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WHO Grade 3/4 Toxicities(n)
Bevacizumab Monotherapy									
Friedman HS et al[59]	Phase 2, multicenter, open-label 1st relapse: n=69 2nd relapse: n=16	Yes	10 mg/kg IV q2wk (28-day cycle)	85	*CR:* 1 *PR:* 23	42.6 (1st relapse 46.4 vs 2nd relapse 27.8)	4.2 (1st relapse 4.4 vs 2nd relapse 3.1)	9.2 (1st relapse 9.1 vs 2nd relapse 9.2)	*Hematologic:* 3 *Nonhematologic:* 36
Kreisl TN et al[60]	Phase 2 1st recurrence; Median age: 53 y; Median KPS: 90	Yes	Initial monotherapy with 10 mg/kg IV q2wk (28-day cycle)	48	*CR:* 1 *PR:* 16	29	3.7	7.2	*Hematologic:* 1 *Nonhematologic:* 12
Raizer JJ et a.[61]	Phase 2	Yes	15 mg/kg q3wk	GB 50	NA	25	NA	6.5	NA
Chamberlain MC et al[62]	Retrospective review, 2005-2008 Pts aged 36-70 y Salvage regimen: PCV:	Yes	10 mg/kg IV q2wk (14-day cycle) (median 2 cycles received)	50	*CR:* 0 *PR:* 21 *SD:* 0 *PD:* 29	42	10	8.5	*Hematologic:* 1 *Nonhematologic:* 11

Reference	Study Design/ Population	TMZ Pre-treatment	Antiangiogenic Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WHO Grade 3/4 Toxicities(n)
	n=21; CYC: n=13; n=13 underwent repeat surgery								
Miscellaneous Antiangiogenic Therapies									
Ahluwalia MS et al [29] Batchelor TT et al[30]	Phase 3, multicenter, double-blind, randomized 1:2:2 Median age: 54 y	Yes	CCNU 110 mg/m^2 q6wk + placebo *or* CED 30 mg/d *or* CED 20 mg/d + CCNU 110 mg/m^2 q6wk	65 131 129	*CR:* 0 *PR:* 5 *SD:* 23 *PD:* 23 *CR:* 1 *PR:* 17 *SD:* 76 *PD:* 10 *CR:* 2 *PR:* 19 *SD:* 67 *PD:* 19	24.5 16 34.5	2.73 3.1 4.2	9.8 8.0 9.4	*Hematologic:* 30 *Nonhematologic:* 16 *Hematologic:* 7 *Nonhematologic:* 66 *Hematologic:* 116 *Nonhematologic:* 57
de Groot JF et al[65]	Phase 2, single-arm, 2007-2008 1st relapse; Median age: 55 y; Median KPS: 90	Yes	Aflibercept (VEGF trap) 4 mg/kg IV on day 1 of q2wk cycle	42	*CR:* 0 *PR:* 7 *SD:* NA *PD:* NA	7.7	2.8	9.1	NA

Reference	Study Design/ Population	TMZ Pre-treatment	Antiangiogenic Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WHO Grade 3/4 Toxicities(n)
Wen PY et al[67,115]	Phase 2 randomized Median age: 55 y; 34% received prior antiangiogenic therapy; 2nd relapse: 34%	NA	XL184 125 mg PO *or* 175 mg qd	78 46	NA	>25 21	NA	NA	NA
Reardon DA et al[68]	Phase 2 randomized, 2004-2005 ≤1 prior chemotherapy regimen; Median age: 52 y; 1st recurrence: 100%	Yes (99%)	CIL 500 mg *or* 2000 mg, 2×/wk on a continuous basis	41[a] 40[a]	*CR:* 0[a] *PR:* 2[a] *SD:* NA *PD:* NA *CR:* 0[a] *PR:* 5[a] *SD:* NA *PD:* NA	10[a] 15[a]	NA	6.5[a] 9.9[a]	*Hematologic:* 5[a] *Nonhematologic:* 2[a] *Hematologic:* 3[a] *Nonhematologic:* 2[a]
Gilbert MR et al[69]	Phase 2, single-agent, randomized Progressive disease following	NA	CIL IV 500 or 2000 mg × 3 doses (on days -8, -4, and -1), followed by resection, then 2000 mg 2×/wk	26	NA	12	1.9	NA	*Hematologic:* 8 *Nonhematologic:* 1

Reference	Study Design/ Population	TMZ Pre-treatment	Antiangiogenic Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WHO Grade 3/4 Toxicities(n)
	radiotherapy; Median age: 54 y								

Abbreviations: CCNU, lomustine; CED, cediranib; CIL, cilengitide; CR, complete response; CYC, cyclophosphamide; GB, glioblastoma; IV, intravenous; KFS, Karnofsky Performance Score; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; PCV, procarbazine, CCNU, and vincristine; PD, progressive disease; PFS, progression-free survival; PR, partial response; pts, patients; SD, stable disease, TMZ, temozolomide.

For the most part, only glioblastoma data are presented in the table. We have reported enrollment numbers for different patient populations only when all data in a paper are presented for combined patient populations.

*The disease progression-free survival and the overall survival were calculated from beginning of retreatment.

[a] Data presented for glioblastoma patients only, except for Reardon 2008,[68] where 6 patients had either anaplastic astrocytoma or low-grade glioma.

Table 5. Temozolomide-Containing Combination Trials in Recurrent or Progressive Glioblastoma[a]

Reference	Study Design/ Population	TMZ Pretreat-ment	Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WHO Grade 3/4 Toxicities (n)
Temozolomide + Bevacizumab Combinations									
Desjardins et al[85]	Phase 2 Median age: 56 y 1st progression: n=15 2nd progression: n=15 3rd progression: n=2	Yes (prior BEV 4 pts)	TMZ 50 mg/m^2/d + BEV 10 mg/kg IV q2wk	32	*CR:* 0 *PR:* 9 *SD:* 16 *PD:* 7	18.8	3.7	8.7	*Hematologic:* 0 *Nonhematologic:* 11 (including 1 grade 5 infection)
Verhoeff JJ et al[70]	Phase 1/2 Median age: 55 y	Yes	TMZ 50 mg/m^2/d q3wk + BEV 10 mg/kg IV q3wk	15	NA	6.7	2.4	3.7	NA
Temozolomide + Nitrosourea Combinations									
Gaviani P et al[73]	Noncomparative, single-arm	Yes	TMZ 150 mg/m^2 on days 1-7 and 15-21 of 28-day cycles + FOT single IV infusion 110 mg/m^2 monthly on day 15	20 (only 10 eval-uable)	NA	40	4.3	NA	*Hematologic:* Severe *Nonhematologic:* NA
Temozolomide + Interferon Combinations									

Reference	Study Design/ Population	TMZ Pretreat-ment	Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WHO Grade 3/4 Toxicities (n)
Groves MD et al[74]	Two phase 2 noncomparative studies Short-acting IFN: Median age: 55 y Median KPS: 80	No	TMZ 150-200 mg/m^2/d for 5 days every month + Short-acting IFN-α2b: 4 MU/ m^2 SC 3x/wk *and*	29	*CR:* 0 *PR:* 4 *SD:* 18	31	3.6	7.2	*Hematologic:* 18 *Nonhematologic:* 10
	PEG-IFN: Median age: 56 y Median KPS: 90		TMZ 150-200 mg/m^2/d × 5 days every month + Long-acting PEG-IFN-α2b SC 0.5 µg/kg/wk	26	*CR:* 0 *PR:* 1 *SD:* 17	38	4.4	10.0	*Hematologic:* 17 *Nonhematologic:* 23
Temozolomide + Miscellaneous Chemotherapy Combinations									
Reardon DA et al[75]	Phase 2, single-arm Median age: 53.6 y	Yes	TMZ continuous daily 50 mg/m²/d + Sorafenib 400 mg 2×/d	32	*CR:* 0 *PR:* 1 *SD:* 15 *PD:* 16	9.4	1.5	9.7	*Hematologic:* 1 *Nonhematologic:* 27
Eisenstat DD et al[82]	Phase 2 Median age: 58 y	Yes (prior chemo-radio-	TMZ 75 mg/m^2 for 21 days per 28-day cycle +	39	*CR:* 1 *PR:* 2 *SD:* 14 *PD:* 17	10	1.5	NA	*Hematologic:* 0 *Nonhematologic:* 11

Reference	Study Design/ Population	TMZ Pretreat-ment	Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WHO Grade 3/4 Toxicities (n)
	1st recurrence: 100%	therapy)	Afatinib 40 mg/d *or* Afatinib 40 mg/d	41	*CR:* 0 *PR:* 1 *SD:* 14 *PD:* 23	3	1.0		*Hematologic:* 5 *Nonhematologic:* 10
			or TMZ 75 mg/m^2 for 21 days per 28-day cycle	39	*CR:* 0 *PR:* 4 *SD:* 21 *PD:* 13	23	1.9		*Hematologic:* 3 *Nonhematologic:* 17
Quinn JA et al[83]	Phase 2, open-label	Yes	TMZ 472 mg/m^2 PO on day 1 of 28-day cycle + O(6)-BG 1-h infusion of 120 mg/m^2, followed immediately by a 48-h infusion of 30 mg/m^2 on day 1 of 28-day cycle	34	*CR:* 0 or 1 *PR:* 0 or 1 *SD:* NA *PD:* NA	9	1.8	4.5	NA[b]
Stockhammer F et al[84]	Retrospective analysis	Yes (except 4	TMZ 10 mg/m^2 bid	28	*CR:* 0 *PR:* 3	43	4.2	16.8	*Hematologic:* 1

Reference	Study Design/ Population	TMZ Pretreat-ment	Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WHO Grade 3/4 Toxicities (n)
	1st recurrence: n=24; 2nd recurrence: n=4	pts)	+ CEL 200 mg/d		*SD:* 15 *PD:* 10				*Nonhematologic:* NA
Boiardi A et al[76]	Nonrandomized, retrospective	No	TMZ 200 mg/m^2 days 1-5 every 28 days + Resection + mitoxantrone, delivered through Rickam reservoir (4 mg/d on days 1-5 q28d) *or* TMZ + resection *or* TMZ 200 mg/m^2 days 1-5 q28d alone	65 50 161	NA	70.7 64 39.3	NA	11 8 5	NA
Reardon DA et al[77]	Phase 1	No	TMZ 200 mg/m^2/d days 1-5 +	91	NA[b]	27.3	12.8	NA[b]	NA[b]

Reference	Study Design/ Population	TMZ Pretreat-ment	Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WHO Grade 3/4 Toxicities (n)
			CPT-11 40 mg/m^2 to 375 mg/m^2 IV on weeks 1, 2, 4, and 5 of each 6-wk cycle						
Chua SL et al[78]	Phase 2, open-label Median age: 55 y 1st relapse	No (prior chemo-therapy: 9%)	TMZ 200 mg/m^2 PO on days 1-5 q4wk + Liposomal DOX 40 mg/m^2 IV on day 1 q4wk	22	*CR:* 1 *PR:* 3 *SD:* 11 *PD:* 7	32	3.6	8.2	*Hematologic:* 8 *Nonhematologic:* 9
Silvani A et al[79]	Phase 2, single-center Median time from 1st diagnosis: 8 mo	No	TMZ 200 mg/m^2 on days 2-6 q4wk + CIS 40 mg/m^2, on days 1 and 2 q4wk	20	*CR:* 0 *PR:* 2 *SD:* NA *PD:* NA	35	NA	NA[b]	NA[b]
Brandes AA et al[80]	Phase 2, multicenter Median age: 53.4 y Median KPS: 80	No (chemo-therapy-naïve)	TMZ 130 mg/m^2 bolus followed by 9 doses of 70 mg/m^2 q12h (total of 5 days) from day 2 q4wk (if no hematologic toxicity dose,	50	*CR:* 1 *PR:* 9 *SD:* NA *PD:* NA	34	4.3	11.2	*Hematologic:* 13 *Nonhematologic:* 4

Reference	Study Design/ Population	TMZ Pretreat-ment	Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WHO Grade 3/4 Toxicities (n)
			increased to 100 mg/m^2) + CIS 75 mg/m^2 on day 1 q4wk						

Abbreviations: BEV, bevacizumab; CEL, celecoxib; CIS, cisplatin; CPT-11, irinotecan; CR, complete response; DOX, doxorubicin; FOT, fotemustine; IFN, interferon; IV, intravenous; KPS, Karnofsky Performance Score; mOS, overall survival; mPFS, median progression-free survival; NA, not available; O(6)-BG, O(6)-benzylguanine; PD, progressive disease; PEG-IFN, PEGylated interferon; PFS, progression-free survival; PR, partial response; SC, subcutaneous; SD, stable disease; TMZ, temozolomide.
For the most part, only glioblastoma data are presented in the table. We have reported enrollment numbers for different patient populations only when all data in a paper are presented for combined patient populations.
*****The disease progression-free survival and the overall survival were calculated from beginning of retreatment with temozolomide.
[a] Data presented for glioblastoma patients only.
[b] Data not available because not presented separately for glioblastoma and other glioma patients

Table 6. Bevacizumab-Containing Combination Trials (Other Than Temozolomide) in Recurrent or Progressive Gioblastoma[a]

Reference	Study Design/ Population	TMZ Pretreat-ment	Bevacizumab Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WHO Grade 3/4 Toxicities (n)
Bevacizumab + Temozolomide Combinations									
Bevacizumab + Miscellaneous Chemotherapy Combinations									
Francesconi AB et al[86]	Retrospective single-center review	Yes	BEV 10 mg/kg IV on day 2 + CP IV on day 1 + ETO phosphate 113.6 mg/m^2 (equivalent to ETO 100 mg/m^2) IV, days 1-3 Treatment repeated q3wk	6	CR: NA PR: 5 SD: NA PD: NA	22	4.4	7.0	*Hematologic:* 2 *Nonhematologic:* NA
Hasselbalch B et al[87]	Phase 2 Recurrent primary (within 6 mo of standard TMZ concomitant and adjuvant therapy)	Yes	BEV 5 mg/kg first 10 pts, then 10 mg/kg IV q2wk + CPT-11 340 mg/m^2 IV if receiving EIAED or if not,125 mg/m^2 q2wk + CET 400 mg/m^2 IV as loading dose, followed by 250 mg/m^2/wk	43 (32 eval-uable)	CR: 2 PR: 9 SD: 17 PD: 4	33	3.7	7.0	*Hematologic:* 4 *Nonhematologic:* 20

Reference	Study Design/ Population	TMZ Pretreat-ment	Bevacizumab Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WHO Grade 3/4 Toxicities (n)
Sathornsumetee S et al[90]	Phase 2, open-label Median age: 52.4 y; 1st relapse: 52%; 2nd relapse: 36%; 3rd relapse: 12%	Yes	BEV IV 10 mg/kg IV q2wk + ERL 500 mg/kg/d IV if receiving EIAED or, if not, 200 mg/kg/d (42-day cycle)	25 (24 eval-uable)	CR: 1 PR: 11 SD: 10 PD: 2	29.2	4.2	10.3	*Hematologic:* 4 *Nonhematologic:* 64
Gilbert MR et al[96]	Phase 2: RTOG 0625 Median age: 57 y; Median KPS: 80	Yes	BEV 10 mg/kg + CPT-11 200 mg/m^2 q2wk	57	*CR:* NA *PR:* NA *SD:* NA *PD:* NA	37	NA	NA	*Hematologic:* 14 *Nonhematologic:* NA
Nghiemphu PL et al[89]	Retrospective chart review, Jul 2005-Jul 2006, single-center BEV cohort: Median age 55 y; Median KPS 90;	Yes	BEV 5 mg/kg q2wk + Chemotherapy: CPT-11: 31 CP: 8 CCNU: 3 ETO: 2 [Dosages not provided]	Chemo therap y w/ BEV: 44 vs Chemo therap y w/o	NA	41 vs 18	4.25 vs 1.82	9.0 vs 6.1	NA

Reference	Study Design/ Population	TMZ Pretreat-ment	Bevacizumab Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WHO Grade 3/4 Toxicities (n)
	1st relapse: 50%; 2nd relapse: 32%; 3rd relapse: 18%			BEV: 79					
Friedman HS et al[59]	Phase 2, multicenter, open-label Median age: 57 y; 1st relapse: 80%; 2nd relapse: 20%	Yes	BEV 10 mg/kg IV q2wk + CPT-11 340 mg/m^2 IV if receiving EIAED or if not, 125 mg/m^2, q2wk	82	CR: 2 PR: 29 SD: NA PD: NA	50.3 (1st relapse: 49; 2nd relapse: 57.1)	5.6	8.7	*Hematologic:* 20 *Nonhematologic:* 62
Narayana A et al[88]	Prospective, consecutive analysis, 2005-2007	Yes (except 1 pt)	BEV IV 10 mg/kg q2wk for 4 doses in 8-wk cycle + CPT-11 125 mg/m^2/d q2w or CP (dose to achieve an AUC = 6 q4wk	GB: 37 AA: 24	CR: 7[a] PR: 32[a] SD: 11[a] PD: 3[a]	44.3[a]	5.0[a]	9.0[a]	NA
Vredenburgh JJ et al[94]	Phase 2	Yes	BEV 10 mg/kg IV q2wk + CPT-11 340 mg/m^2	23	CR: 1 PR: 13 SD: 8 PD: 1	30	4.7	9.3	NA

Reference	Study Design/ Population	TMZ Pretreat-ment	Bevacizumab Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WHO Grade 3/4 Toxicities (n)
			IV if receiving EIAED or if not, 125 mg/m^2, q2wk						
Vredenburgh JJ et al[92]	Phase 2 *Both cohorts:* Median age 48 y; Median number of progressions 2	Yes	*Cohort 1*: BEV 10 mg/kg IV q2wk + CPT-11 340 mg/m^2 IV if receiving EIAED or if not, 125 mg/m^2, q2wk (6-wk cycle) *Cohort 2*: BEV 15 mg/kg IV q21d + CPT-11 340 mg/m^2 IV if receiving EIAED or if not, 125 mg/m^2 on days 1, 8, 22, and 29 (6-wk cycle)	23 (35 total) 12	NA	46[c]	5.6[c]	9.8[c]	NA

Reference	Study Design/ Population	TMZ Pretreat-ment	Bevacizumab Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WHO Grade 3/4 Toxicities (n)
Reardon DA et al[91]	Phase 2, open-label Median age: 54.3 y; 1st relapse: 52%; 2nd relapse: 30%;3rd relapse: 19%	NA	BEV 10 mg/kg IV q2w + ETO 50 mg/m^2 daily for 21 consecutive days each month	27	CR: 1 PR: 5 SD: 19 PD: 2	44.4	4.2	10.8	*Hematologic:* 15 *Nonhematologic:* 17 (including 1 grade 5 thrombosis) [includes only those AEs that occurred in ≥10% of pts]
Stark-Vance V[97]	NA	NA	BEV 5 mg/kg every other wk for 2 doses + CPT-11 125 mg/m^2 qwk for 4 doses, followed by 2-wk rest period	GB 11; 10 other gliomas	CR: 1[a] PR: 8[a] SD: 11[a] PD: 1[a]	NA	NA	NA	NA
Pope WB et al[93]	Retrospective database review	NA	BEV + CP, CPT-11, or ETO [dosages NA]	10	CR: 0 PR: 4 SD: 3 PD: 3	NA	NA	NA	NA
Norden AD et al[95]	Retrospective analysis Jun 2005-Mar 2007	Yes	BEV 10 m/kg (1 pt received 5 mg/kg) q2wk + Chemotherapy:	33	NA[b]	42	NA[b]	NA[b]	NA[b]

Reference	Study Design/ Population	TMZ Pretreat-ment	Bevacizumab Regimen	n	Radio-graphic Response (%)	6-mo PFS* (%)	mPFS* (mo)	mOS* (mo)	WHO Grade 3/4 Toxicities (n)
	Median age 50 y; Median KPS 80		CPT-11: n=47 CP: n=6 BCNU: n=1 TMZ: n=1						
Gutin PH et al[98]	Cohort study Median age 56 y; Median KPS 90	NA	BEV 10 mg/kg IV q2wk (28-day cycle) (median, 7 cycles) + 30 Gy HFSRT in 5 fractions after first BEV cycle	20	NA[b]	65	7.3	12.5	NA[b]

Abbreviations: AA, anaplastic astrocytoma; AUC, area under the curve; BCNU, carmustine; BEV, bevacizumab; CET, cetuximab; CP, carboplatin; CPT-11, irinotecan; CR, complete response; EIAED, enzyme-inducing antiepileptic drugs; ERL, erlotinib; ETO, etoposide; GB, glioblastoma; HFSRT, hypofractionated stereotactic reirradiation; inst, institution; IV, intravenous; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; PD, progressive disease; PFS, progression-free survival; PR, partial response; pts, patients; SD, stable disease.

For the most part, only glioblastoma data are presented in the table. We have reported enrollment numbers for different patient populations only when all data in a paper are presented for combined patient populations.

*The disease progression-free survival and the overall survival were calculated from beginning of retreatment.

[a] Data presented for glioblastoma patients only, except for Narayana 2009 study,[88] where 37 patients had glioblastoma and 24 patients had anaplastic astrocytoma, and Stark-Vance et al,[97] where 11 patients had glioblastoma and 10 had other high-grade gliomas.

[b] Data not available because not presented separately for glioblastoma, anaplastic astrocytoma, and other glioma patients.

[c] Data presented for both cohorts combined.